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CEREBRO-SPINAL FEVER
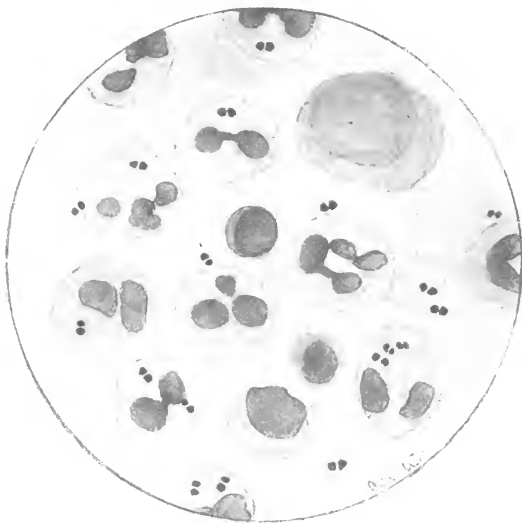
PLATE I.

Film of centrifugalised deposit of cerebro-spinal fluid in an
acute case of cerebro-spinal fever.   Showing polymor-
phonuclear cells, lymphocytes, and one large endothelial
cell.   Meningococci are seen intra- and extra-cellular.
(Gram-fuchsin preparation seen under oil-immersion ob-
jective and high-power eyepiece.)

Frontispiece.

CEREBRO-SPINAL FEVER

THE ETIOLOGY, SYMPTOMATOLOGY, DIAGNOSIS AND TREATMENT OF EPIDEMIC CEREBRO-SPINAL MENINGITIS

BY

C. WORSTER-DROUGHT, M.A., M.B. Cantab.

CAPTAIN (TEMP.), R.A.M.C.

OFFICER-IN-CHARGE CEREBRO-SPINAL FEVER WARD, AND NEUROLOGIST TO THE ROYAL HERBERT HOSPITAL, WOOLWICH
MEDICAL REGISTRAR, WEST END HOSPITAL FOR NERVOUS DISEASES

AND

ALEX. MILLS KENNEDY, M.D. Glasg.

CAPTAIN, LATE R.A.M.C.

LATE OFFICER-IN-CHARGE CEREBRO-SPINAL FEVER LABORATORY, AND BACTERIOLOGIST TO THE ROYAL HERBERT HOSPITAL, WOOLWICH

CONTAINING EIGHT FULL-PAGE PLATES AND FIFTY-SIX LINE ILLUSTRATIONS AND CHARTS

PREFACE

DURING the past few years a considerable amount of progress has been made in the diagnosis and treatment of cerebro-spinal fever. The outbreak of this disease in England in 1915 and the methods adopted to combat it afforded exceptional opportunities for its study.

The authors of this volume were fortunately placed for the study and investigation of cerebro-spinal fever in that the one was a practising neurologist and the other a professional pathologist and bacteriologist. Being posted for duty at Woolwich they became responsible for the investigation, prevention and treatment of cerebro-spinal fever among the troops in the Woolwich military district. In the following pages are given the results of these investigations and observations extending over a period of three years, together with some observations upon cases which they had previously seen in civil life. In addition, the literature dealing with the disease has been consulted, and all work necessary to bring the subject thoroughly up to date has been incorporated. A full bibliography is appended.

As the bulk of the work has been carried out while the authors were actively engaged in military duties, they are conscious that many imperfections may have crept into the text as a consequence. Nevertheless they hope that the book will prove useful to those who at any time may have to deal with an outbreak of cerebro-spinal fever either in an epidemic or sporadic form. The large number of troops at present mobilised in this country and America, as well as those that are returning from the various seats of war, render it an opportune time for the appearance of this book.

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CHAPTER I

Definition.—Cerebro-spinal fever may be defined as an infectious, contagious disease, occurring both sporadically and in epidemics, and caused by the meningococcus (Diplococcus intracellularis meningitidis of Weichselbaum). The organism, as a rule, localises in the meninges of the brain and spinal cord, with consequent inflammation of these parts and resulting in various constitutional and local disturbances.

The disease has received many names, both popular and scientific. Prior to the year 1914, the term " epidemic cerebro-spinal meningitis " was much in use; apart from its being cumbersome, however, this name does not accurately define the disease, since many cases are not epidemic but sporadic. " Meningococcal meningitis " has also been employed, and although pathologically accurate, the name conveys no hint of the relationship of the disease to the acute specific fevers. The term " cerebro-spinal fever " has the merit not only of drawing attention to this fact, but also of indicating the site of the essential pathological lesion; moreover, it is the name which at the present time is in most frequent use.

Geographical Distribution.—A survey of the history of cerebro-spinal fever shows that epidemics have occurred in almost all parts of the world. On the whole, the disease appears rather more prevalent in the temperate zone of the Northern hemisphere, particularly in the countries of Central Europe and the Eastern States of America; the Southern hemisphere, however, is by no means free. In the East, the countries principally affected are Asia Minor and Syria. Epidemics have also occurred even in tropical regions—the Soudan, West and East Africa, and in India the disease is not entirely unknown.

In the United States of America, epidemics have recurred since

1808, chiefly in New York, Boston, California and Texas. Prior to 1866, when an outbreak occurred at Bardney near Lincoln, little was known of cerebro-spinal fever in the British Isles, and although small outbreaks occurred from time to time, it was not until 1907 that a more serious epidemic appeared in Belfast; almost simultaneously many cases of the disease occurred in Glasgow. During the early months of 1915, when troops were quartered all over the country, the first epidemic affecting England as a whole was experienced. It has been suggested that a fresh strain of infection was brought over from Canada by the first Canadian contingent arriving in this country. Until 1915, Australia had escaped with only a few scattered cases of the disease, or very small epidemics.

Seasonal Prevalence. — Cerebro - spinal fever is essentially a disease of winter and spring. Of 85 American epidemics recorded by Hirsch, 37 occurred in winter, 18 in winter and spring, and 23 in spring ; of 63 French epidemics, 24 prevailed in winter, 17 in winter and spring, and 9 in spring. According to Aitken, 311 of 417 outbreaks in Sweden commenced during the winter. In Germany, during the successive years 1905–8, four-fifths of all cases recorded occurred in the winter and spring months, while of 12 epidemics affecting Great Britain and Ireland, 11 fell within the same seasonal periods.

The majority of recorded epidemics have begun during one of the four months December, January, February and March, the maximum intensity of the outbreak being reached in April or May ; from this latter month the number of cases, as a rule, steadily declines, and the epidemic is usually over by the end of July. The epidemic in New York of 1904 began in March and reached its height in May, declining in June and disappearing in July ; in the following year, the epidemic commenced in February, its maximum intensity occurring towards the end of March. In England and Wales the recent general outbreak began in January 1915, increasing to a maximum during March and April ; it then declined rapidly in June, and reached its minimum towards the end of July. In our own district no military case was reported from July 1915 until October 1915, when one case occurred ; this was apparently an isolated instance, for no other case appeared until the middle of December. From this time onwards the number of cases followed the usual seasonal prevalence, reaching its highest in April 1916, and falling off towards the end of June, July being the only month of 1916 that we received no case. A few only occurred during each

of the months August, September, October and November, but during December the incidence exhibited a sharp rise. Then followed a steady increase in the number of cases throughout January and February 1917, the maximum being reached in March ; the case incidence, however, declined during April and fell to a minimum in May. Each of the months June, July, August and September 1917 yielded a few cases, but in October none occurred.

The possible influence of climatic conditions as a predisposing cause of the disease is discussed in Chapter IV. (p. 41).

Age Incidence.—In most epidemics the greater number of cases have occurred in children below the age of fifteen years. From the statistics available, it would appear that children under ten years are the most susceptible ; the proportion of cases at this age period occurring in New York during the years 1905, 1906 and 1907 was as follows :

1905	.	.	.	2180 cases ;	67	per cent under	10 years.
1906	.	.	.	993	,,	65	,,	,,	10	,,
1907	.	.	.	828	,,	68	,,	,,	10	,,

In the Prussian epidemics of 1905–7, of 8198 cases 80·12 per cent were below the age of sixteen years, while the proportion of sporadic cases under five years occurring in England and Wales during 1913 was 43·1 per cent, and during 1914, 51·3 per cent.

In a few epidemics, however, the number of patients over 20 years of age have outnumbered those younger ; for instance, this was the case in the epidemic at Montgomery, Alabama, in 1848. In the Victorian epidemic, Australia, 1915, only 29·9 per cent of cases occurred in children under the age of 10 years. Further, in many military epidemics children have escaped almost entirely.

A superficial examination of the recorded figures of age incidence during the recent outbreaks in England and Wales would suggest that the most susceptible age is between 20 and 25 years. Compton, however, in a recent communication, points out that the true age of greatest susceptibility is arrived at by referring the percentage of cases at each age period to the number of people of that age period living in the particular district at the time of the outbreak. This latter figure was estimated by taking the combined statistics of the contacts. From the data thus obtained, Compton concluded that the most susceptible age is under five years and the least susceptible from 35 to 40 years.

Over 50 years of age the disease is somewhat uncommon. One

of our patients was aged 60, while Fairley and Stewart mention a case developing cerebro-spinal fever at the age of 84.

Of purely military cases, the age incidence in 136 patients of our series was as follows :

15 to 20 inclusive	.	.	.	40·5	per cent.
21 ,, 25	,,	.	.	.	32·4	,,
26 ,, 30	,,	.	.	.	16·2	,,
31 ,, 35	,,	.	.	.	2·9	,,
36 ,, 40	,,	.	.	.	5·1	,,
40 ,, 50	,,	.	.	.	2·2	,,
50 ,, 60	,,	.	.	.	·7	,,

The extreme limits of age between which the cases occurred was 15 and 60 years ; with the exception of 15, all patients were under 31 years.

Sex Incidence.—Although there is no striking difference between the number of cases that occurs in the two sexes, the proportion of males attacked shows a slight preponderance over that of females. Thus, in 1906, of 1026 cases occurring in New York City 611 were males and 415 females ; in the Texas epidemic 1598 of 2575 cases were males and 977 females. During the Victorian epidemic of 1915 Fairley and Stewart give 2·4 : 1 as the ratio of male to female cases for the whole state of Victoria. Also, in London boroughs, during the first half of 1915, of 468 cases 257 were male and 211 female (R. J. Reece).

Race Incidence.—The relative incidence of the disease among whites and negroes, in regions inhabited by both, has usually shown that negroes were chiefly affected. This appears to have been the case in the following epidemics : New Orleans (1850), Memphis (1862–63), Mississippi (1862–63), Maryland (1864), Philadelphia (1867) and South Carolina (1873). In the Texas epidemic (1912), however, a much greater proportion of whites were attacked ; of 2135 cases tabulated by Steiner, 1600 were whites and 535 negroes. In reality, the question is probably not so much one of actual race as of hygienic conditions.

CHAPTER II

THE MENINGOCOCCUS AND ALLIED ORGANISMS

THE meningococcus was discovered in 1887 by Weichselbaum, who isolated the organism from the meningeal exudate of cases of meningitis occurring in epidemic form at Vienna. For a time some doubt was cast upon Weichselbaum's work by Jaeger, Heubner and others ; subsequent investigations, however, have confirmed the truth of Weichselbaum's original statements, and the meningococcus is now almost universally accepted as the causative organism of cerebro-spinal fever.

The meningococcus is a member of a group of cocci, having a number of common characteristics (staining reactions and morphology), and usually referred to as the *Gram-negative Cocci*. With one exception, the gonococcus, all these cocci may be found in the naso-pharynx of healthy people ; hence their differentiation is an extremely important bacteriological problem in controlling the epidemic spread of cerebro-spinal fever.

The members of the group of Gram-negative Cocci are :

1. Meningococcus (including the parameningococcus of Dopter).
2. Gonococcus.
3. Micrococcus flavus.
4. Micrococcus catarrhalis.
5. Micrococcus pharyngis siccus.
6. Diplococcus mucosus capsulatus.

MENINGOCOCCUS

The meningococcus or Diplococcus intracellularis meningitidis is a micrococcus about 1μ in diameter, being larger than the gonococcus, but somewhat smaller than the Micrococcus catarrhalis, and is non-capsulated. The meningococci have a diplococcal arrangement and

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usually show definite flattening of their adjacent edges, thus presenting a kidney-bean appearance ; occasionally groups of four are seen, but regular masses or chains are never found. On direct microscopical examination of the cerebro-spinal fluid from a case of cerebro-spinal fever, forms with flattening of one side are the rule ; in cultures, however, particularly when over twenty-four hours old, spherical forms often predominate.

The organism is fairly constant in its morphological appearance, but variation in size is not infrequent. In some cases, as seen on direct examination of films of the cerebro-spinal fluid, the cocci are larger than in others ; occasionally these larger forms are met with in association with the smaller. The larger cocci appear to be merely swollen involution forms. In culture, variation in size is fairly common, especially when the organisms are obtained from the naso-pharynx. Swollen involution and degenerate forms are frequent in older cultures.

Staining Reactions.—The organism is easily stained with any of the basic aniline dyes and takes up the stain with fair uniformity ; the larger and involution forms often overstain, while cocci from old cultures stain badly. Meningococci are invariably Gram-negative, and Gram-positive individuals are never observed.

The technique of the Gram staining which we have invariably used is as follows :

A film of the centrifugalised deposit from the cerebro-spinal fluid, or of the culture, is made in the usual way, dried in the air and fixed by passing quickly two or three times through a Bunsen flame. It is then stained for about three minutes with a fresh saturated alcoholic solution of gentian violet in aniline oil water, the stain being filtered on to the film. The excess of stain is poured off and Gram's iodine solution added direct, the solution being allowed to act for $\frac{1}{2}$ to 1 minute. Following this, the iodine solution is poured off and the preparation dried with clean blotting-paper. The film is then decolourised with absolute alcohol, several washings being applied, until the colour has almost wholly disappeared ; it is afterwards washed in water. Dilute carbol-fuchsin is finally filtered on to the preparation for 20 to 30 seconds to act as a counter-stain and the slide washed in water and dried.

Aniline oil water is prepared as follows : 5 c.c. aniline oil added to 100 c.c. distilled water and repeatedly shaken until as much oil as possible has dissolved. It is kept in a dark glass bottle and filtered before use.

Gram's gentian violet is prepared as follows : one part of a saturated solution of gentian violet in alcohol is added to 10 parts of the aniline oil water.

For cerebro-spinal fluid we have found Leishman's modification of the Romanowsky method a most useful staining reaction. The stain consists of eosinate of methylene blue dissolved in pure methyl alcohol free from acetone. (The stain can also be obtained in " Soloid " form.)

A film of the centrifugalised deposit of the cerebro-spinal fluid is made and dried in the air without heating. Leishman's stain is then filtered on and allowed to act for about five minutes, care being taken not to allow the preparation to dry. At the end of this time distilled water is added to dilute the stain, the whole being mixed by means of a glass rod. The diluted stain is allowed to act for 10 to 15 minutes, after which it is washed off with distilled water and the preparation dried quickly without heating.

With Leishman's stain the meningococci are stained blue and the different cells present have characteristic appearances. Neutrophile, eosinophile and basophile granules are shown up distinctly, the nuclear characteristics are apparent, and red blood-cells, when present, can easily be distinguished by their pinkish colour. Leishman's stain also enables the progress of the cellular reaction to be followed. In an established case of cerebro-spinal fever the polymorphonuclear cells contained in the fluid withdrawn at the first lumbar puncture are usually degenerate, the cytoplasm being disintegrated, the nuclei staining poorly and the granules appearing indistinct. As the patient improves, fresh and more healthy leucocytes appear, their nuclei staining well and their granules becoming more and more distinct. A similar result is observed as a reaction to the intrathecal administration of serum ; this latter reaction is important as it occurs quite apart from infection and will often render a clear cerebro-spinal fluid turbid. For example, in a case of tetanus treated by the intrathecal administration of anti-tetanic serum, the cerebro-spinal fluid withdrawn on the day following the intrathecal injection of serum is distinctly turbid, though sterile, while that obtained prior to the administration of serum is perfectly clear. The turbidity is found to be due to the presence of fresh, well-preserved and clearly-staining polymorphonuclear leucocytes.

In a case of meningococcal meningitis the diplococci may be found intracellular, extracellular, or both ; in some cases the majority of cocci are intracellular, in others extracellular. As a general rule, extracellular cocci are indicative of severity in the disease-process. In many cases the organisms are abundant and

easily seen, but in others prolonged search is frequently necessary, particularly in subacute cases or in cases not examined until late in the disease.

Cultural Requirements.—The meningococcus can be cultivated outside the body with comparative ease under certain conditions. The organism is practically an obligatory aërobe, and growth as a rule will only occur between the temperatures of 25° C. and 42° C., the optimum temperature being 37° C. Media containing serum or blood are practically always necessary to ensure growth in primary cultures. Not infrequently, it is somewhat difficult to obtain the primary culture from the cerebro-spinal fluid, but once a growth is obtained subcultures grow readily, sometimes even on ordinary media. Blood or haemoglobin is most useful in promoting the growth of meningococci, hence one of the most reliable methods for ensuring primary cultures is to smear the surface of the medium with a few drops of fresh human blood.

A variety of media have been described for the cultivation of the meningococcus. That which we have used most extensively is " trypagar " enriched with 2 per cent horse serum, ascitic fluid or blood solution. This medium—trypsin broth legumin agar—was arrived at by Gordon and Hine as the result of an experimental study of the cultural requirements of the meningococcus. It has many advantages: on "trypagar" cultures grow well and the colonies are large ; it is transparent, thus rendering the recognition of the colonies easy ; also, the medium is inexpensive and not difficult to prepare. Subcultures frequently grow on it without enrichment. The organism, however, does not as a rule live on " trypagar " for more than 48 hours. In order to prolong its vitality, Flack suggested adding extract of wheat germ to the " trypagar," and, in experiments, succeeded in keeping meningococci alive for 10-28 days ; in subculture the organism occasionally lived for as long as two months. In trypsin broth containing a little serum Gordon has kept stock cultures alive for three weeks.

Preparation of " Trypagar " (Gordon and Hine).

Trypsin broth (Douglas)	.	.	.	c.c.	1000.
Agar fibre	.	.	.	gms.	20.
Calcium chloride	.	.	.	gms.	0·125.

Dissolve in autoclave at 118° C. for ¾ hour. Place in saucepan, and, while boiling, titrate with N/10KOH, using phenolphthalein as indicator ; add sufficient KOH to render neutral. Cool to 60° C., add

the white of two eggs beaten up with shells, and place in steamer for two hours or in autoclave at 118° C. for ¾ hour.   Filter, and to filtrate add—

<div style="text-align:center">Sterile pea extract   .   .   .   c.c. 50.</div>

Sterilise in the usual way.

The ingredients of " trypagar " are prepared as follows :

Trypsin Broth (Douglas).

Fresh bullock's heart, free from fat and vessels
      and finely minced   .   .   .   .   gms. 500.
    Water   .   .   .   .   .   .   c.c. 1000.

Make faintly alkaline to litmus with 20 per cent KOH solution. Heat slowly to 75°-80° C. for 5 minutes.   Cool to 37° C.   Add—

Liquor Trypsinae Co. (Allen and Hanbury) 1 per cent, and keep at 37° C. for 2½ to 3 hours until trypsinisation is complete as shown by the biuret test.

Make slightly acid with glacial acetic acid and boil slowly for 15 minutes.

Leave overnight in a cool place, and then syphon off the supernatant clear fluid and render faintly alkaline to litmus.   Sterilise in autoclave at 118° C. for one hour on each of two days.

Biuret Test for Peptone.

To 5 c.c. of the broth add 0·1 c.c. of 5 per cent solution of copper sulphate ; then add 5 c.c. $N/1NaOH$.

Pink colour .   .   .   .   Trypsinisation complete.
Bluish-purple colour   .   .   Trypsinisation incomplete.

Peaflour Extract

<div style="text-align:center">(preferably freshly made for each batch of agar).</div>

Ordinary peaflour .   .   .   gms. 100.
Salt .   .   .   .   .   gms. 100.
Distilled water   .   .   .   c.c. 1000.

Mix and steam for ½ hour, stirring occasionally.   Allow to settle and filter.

Agar.

Weigh, cut into small pieces with scissors, place in a large vessel, and wash twice with water quickly.   Drain off thoroughly, add just sufficient acidulated water to cover (water containing 2·5 c.c. glacial acetic acid per litre constitutes the acidulated water).   Mix well, leave for 15 minutes, then pour off water and wash thoroughly several times to get rid of all acid.   Allow to drain.

For primary cultures the " trypagar " must be enriched by the addition of 2 per cent serum or blood solution.

Horse Serum

(etherised to preserve sterility).

Two per cent of sterile serum is added to the medium after melting and cooling to 45° C.

Sterile Solution of Rabbit's Blood.

This consists of a 5 per cent solution of sterile blood in citrated saline with ether added as an antiseptic. Two per cent of this blood solution is added to the medium after melting and cooling to 45° C. It is said to be superior to serum for ensuring primary cultures.

Other culture media for the meningococcus are as follows :

" **Nasgar.**"—This medium has had considerable vogue in this country ; it is a nutrose ascitic agar which was introduced by Gordon for the isolation of the meningococcus prior to the appearance of " trypagar." " Nasgar " is not as good as " trypagar," but when smeared with a few drops of fresh human blood primary cultures are usually successful.

Preparation of "Nasgar."

Ascitic fluid .	.	.	.	c.c. 15.
Distilled water	.	.	.	c.c. 35.
Nutrose	.	.	.	gms. 1.

Boil in a flask and filter. One part of filtrate is added to two parts of ordinary agar. Steam for $\frac{1}{2}$ hour and place in tubes.

The vitality of the meningococcus on " nasgar " as a rule is short, the organism living for 48 hours at the most.

M'Intosh found that a medium composed of three parts of 3 per cent agar neutral to phenolphthalein, and one part of serum was very satisfactory and better than " nasgar."

Sophian used a beef or veal infusion agar neutral to phenolphthalein, and containing 10 per cent of glucose ; to this was added ascitic fluid or sheep serum in the proportion of 1 to 6.

Kutscher's serum agar, made from placental extract, has been used by a number of workers and found fairly satisfactory.

Solidified egg is a useful culture medium, and growth usually occurs readily as a smooth and shiny layer.

In serum broth the organism grows well, producing a general turbidity and, in a few days, some deposit.

For blood cultures we have found 10 c.c. of the patient's blood added to 50 c.c. of ordinary bouillon to be quite satisfactory, growth appearing on the second or third day as a very slight turbidity.

Appearance of Colonies.—At the end of twenty-four hours' incubation at 37° C. on " enriched trypagar," the appearance of meningococcus colonies is characteristic. They are seen as clear, translucent, bluish-grey, circular discs, being about 2 mm. in diameter and raised above the surface of the medium with distinct and regular margins ; they are moist, emulsifying readily in saline, and although very slightly viscid, are not friable. After 48 hours' incubation at 37° C. the colonies are larger and tend to be somewhat opaque, the centre appearing more granular ; the periphery, however, continues to show the clear bluish-grey colour. Colonies of meningococci usually remain discrete, but when the medium has been heavily inoculated, as in subculture or in cultures from naso-pharyngeal swabs, they tend to become confluent, the growth appearing as rather a thick mucoid smear ; within twenty-four hours, however, the typical bluish-grey translucent appearance is always distinctive. Meningococcus colonies are much larger than those of either the pneumococcus or streptococcus.

Fermentation Reactions.—A considerable amount of investigation has been carried out on the fermentation reactions of the meningococcus and their relative value in the identification of the organism.

Lingelsheim (1906), Buchanan (1907), Shennan and Ritchie (1908), Mayer (1909), Martin (1910), Griffith (1916) and Scott (1916), all using solid media, ascitic agar or solidified serum medium, found acid produced on glucose and maltose but on none of the other sugars. Gordon (1907), using an ascitic broth, obtained acid with glucose, maltose and galactose, but not with saccharose. Arkwright in the same year, using liquid media, found acid produced with maltose and usually with glucose, galactose and laevulose, but not with saccharose. Buchanan noted that after a certain period in a fluid medium (ascitic fluid), acid was produced from galactose, whereas with a solid medium containing galactose acid was produced in almost negligible quantities on rare occasions only. Shennan and Ritchie also found that with galactose acid was produced in liquid media but not on solid. In 1909, however, Symmers and Wilson, using ascitic broth, found acid production with glucose and maltose but not with other sugars.

Elser and Huntoon, in 1909, made a most thorough investigation of the fermentation reactions of the meningococcus, testing 200 strains. With an ascitic agar, acid was obtained on glucose and maltose only ; also, these observers showed that galactose is an unstable sugar and may undergo partial decomposition on heating ;

in this way they explained the varying results previously obtained with the use of liquid media. Elser and Huntoon found that, as a rule, a greater acid production took place from maltose than glucose, although in a few instances an exactly opposite condition resulted. Generally, acid production was obtained within twenty-four hours on solid media, whereas with liquid media 48 hours and sometimes 72 hours were required.

Griffith (1916) found that meningococci recently isolated from cerebro-spinal fluid seldom produced equal amounts of acid from glucose and maltose ; some cultures fermented glucose more strongly than maltose, while others behaved in the reverse manner. After repeated subcultivation, however, this author found that in most cases these differences disappeared. Naso-pharyngeal strains, on the other hand, usually fermented both sugars equally. Scott (1916) found that of strains isolated from the cerebro-spinal fluid as well as from the naso-pharynx, some fermented glucose more strongly than maltose ; others yielded an opposite result, and a few fermented the two sugars equally.

It would thus appear that a certain amount of care is necessary in the choice and preparation of the medium. Solid media, containing serum in some form, yield the most constant results, viz. acid with glucose and maltose but not with saccharose, lactose, mannit, laevulose, galactose or inulin. If liquid media be used, however, acid may be produced with galactose, and possibly also with laevulose. Further, while some observers have found no appreciable difference in the amount of acid produced with glucose and with maltose, others differ as to which sugar yields the greater acid production.

For fermentation tests we have invariably employed a serum agar prepared with hydrocele fluid—2 per cent of hydrocele fluid and 1 per cent of the sugar, with litmus added as the indicator.

Viability.—External to the human body the meningococcus appears to be a delicate organism. In most media it perishes within a few days ; Gordon, however, was able to keep colonies alive for three weeks in trypsin broth containing a little serum. In sealed egg tubes meningococci retain their viability for several weeks and have been successfully subcultured after seven months (Griffith).

The optimum temperature for growth of the organism is 37° C., and it is usually stated that failure to grow at 23° C. is of diagnostic value ; this, however, must not be taken as an absolute test but rather for confirmatory purposes, as growth at 23° C. appears

largely to depend upon the media employed. On ascitic agar growth rarely occurs at 23° C. ; on " trypagar " a few strains may exhibit a certain degree of growth, but the majority show none. On egg media, however, the organism frequently grows at 23° C. in 2 to 4 days, and, with media containing haemoglobin, cultures may occasionally be obtained.

The meningococcus is very susceptible to drying. At room temperature in daylight the organism appears to die within one hour, and it has even been stated that actual desiccation for 2 to 5 minutes is sufficient to produce the same result. If moisture be present, however, meningococci may live in daylight for two hours or longer. Bright sunlight has less effect upon the organism than drying, as half an hour's exposure fails to destroy it.

The organism is one which tends quickly to undergo disintegration by a process of autolysis ; this process has been shown by Flexner to depend upon an intracellular enzyme. Although exposure to a temperature of 60° C. for ten minutes will certainly destroy the organism, heating to 65° C. is necessary to inactivate the enzyme.

Gordon has pointed out that normal saliva inhibits the growth of the meningococcus, whereas nasal mucus has no such inhibitory action ; further, this observer has demonstrated that the saliva owes its inhibitory action upon the organism to streptococci, the degree of inhibition being proportional to the number of streptococci present in the saliva. The process therefore is an example of bacterial antagonism. Colebrook (1915) has demonstrated that the pneumococcus also has a similar antagonistic action on the growth of the meningococcus.

Serum Reactions.—(1) *Agglutination.*—The specific agglutinins of the meningococcus have been the subject of much careful investigation. As a result it has been shown that differences exist between the reactions of different strains of the organism. From a study of these variations and the application of " absorption " methods, it has been possible to differentiate the majority of strains into groups or " types " ; at present, however, it is not finally settled as to whether this grouping is complete.

Lingelsheim, testing a large number of strains isolated during an epidemic of cerebro-spinal fever in Upper Silesia (1904–5), found that all were agglutinated by one or the other of two monovalent sera which had been prepared from rabbits treated with two strains obtained from the cerebro-spinal fluid of cases suffering from the

disease. Kutscher, in 1906, using an anti-meningococcal horse serum, tested a few cerebro-spinal and naso-pharyngeal strains and found that all agglutinated. Applying the " absorption " of agglutinin test, he discovered that the agglutinin for only some of the strains was absorbed. In 1908 Eberle described variations in the degree of agglutinability of the various strains which he tested, some agglutinating very poorly and others exceedingly well. Ark-wright (1909), employing an anti-meningococcal horse serum, reported the result of an investigation of 25 strains ; he also found variations in the degree of agglutinability of different strains, some absorbing their own agglutinin, but not that of other strains. At about the same time, variations in the degree of agglutinability of different strains were noted by Friese, Muller and Lieberknecht. Elser and Huntoon, also in 1909, reported the result of their investigations ; using sera prepared from rabbits, these observers found variations in the agglutinability of individual strains and considerable differences in the degree of agglutinability of different strains with the same serum, some strains being in-agglutinable. As a rule, the latter were able to absorb agglutinin.

In the same year (1909), Dopter reported the discovery of his " parameningococcus " ; subsequently, he described twelve cases of typical cerebro-spinal fever due to this organism. The " para-meningococcus," isolated from the cases, failed to agglutinate with anti-meningococcal serum ; also, anti-meningococcal serum ex-hibited no beneficial therapeutic effect upon the cases clinically, but a special anti-parameningococcal serum proved most successful. Five years later, Dopter and Pauron reported the results of a further study of the " parameningococcus." They found that anti-parameningococcal serum frequently agglutinated meningococci as well as parameningococci, but that differentiation could be effected by means of absorption tests. By further application of absorption methods they were able to separate the parameningococci into three groups ; the first group comprised those most commonly met with, while the members of the third group were rare.

In 1911 Sachs-Muke, when studying naso-pharyngeal strains of the meningococcus, found variations in the degree of agglutin-ability and also some inagglutinable strains.

In 1915 Gordon and Murray investigated by means of agglutina-tion and " absorption of agglutinin " tests the strains isolated from the cerebro-spinal fluid of 32 cases of cerebro-spinal fever ; they were able to differentiate four main groups or " types " of the

meningococcus. The method employed was as follows : A rabbit was prepared against the first eight strains of the series of 32 cocci. All the 32 strains were then put up against the rabbit's serum, with the result that 19 of them exhibited good agglutination and also absorbed the specific meningococcus agglutinin from the serum. The remaining 13, however, failed to absorb the specific agglutinin. Consequently, the 19 cocci that had shown good agglutination were classified as "Type I." Gordon and Murray next prepared a rabbit against the 13 cocci negative to "Type I." serum ; in the same way the 32 strains were tested against the resulting serum. It was found that seven showed marked agglutination and absorbed the specific agglutinin, while one of the cocci, which had exhibited slight agglutination only, also absorbed the specific agglutinin. These eight cocci were therefore grouped as "Type II." A third rabbit was now prepared against the five remaining cocci, and again the 32 strains were put up against the serum ; the result was that while 24 of the cocci showed some agglutination, it was very slight in all excepting in the case of 13 "Type I." cocci and four of the five as yet unclassified strains. The absorption test proved that one of the specimens of "Type I." and the four cocci still unclassified, that had agglutinated so well with this serum, absorbed the specific agglutinin therefrom. These four cocci were therefore classified as "Type III.," while the one meningococcus that had reacted to both "Type I." and "Type III." agglutinin was termed "amphoteric." A fourth rabbit was then prepared against the one remaining coccus, and all the 32 strains tested against its serum ; it was proved that this coccus alone was agglutinated and alone absorbed the specific agglutinin from the serum. This coccus was termed "Type IV."

On applying the agglutination test, with the four "type" sera obtained by the above methods, to strains isolated from the naso-pharynx and which had answered the cultural and fermentation tests for the meningococcus, Gordon found that while the majority of these naso-pharyngeal organisms could be identified with the meningococcus of one or another "type," several of them could not. Further, on preparing specific agglutinating sera univalent against individual specimens of these "pseudo-meningococci," it was found that although the cocci in question excited, in some cases, the production of group-agglutinin for one or another kind of meningococcus, their specific agglutinin, while exhibiting a specific affinity for the individual homologous "pseudo-meningococcus," possessed

no such affinity for any of the four " types " of meningococcus previously classified. Consequently, it was clear that these organisms (pseudo-meningococci or pharyngococci) were quite different from any of the four " types " of cocci isolated from cerebro-spinal fluid. From the evidence thus obtained, Gordon concluded that the prevalent outbreaks of cerebro-spinal fever in this country (1915–16) were due not to transient and unstable variants of a single micro-organism, but to a group of individual species (provisionally four) of meningococcus. It was not assumed, however, that the limit of their individual variation had fully been defined.

According to Flexner, Gordon's Type I. appears to correspond with the " parameningococcus " of Dopter, and Type II. with the normal or regular meningococcus. Types III. and IV. appear to conform to the more common intermediates.

Investigations carried out with Gordon's monovalent " type " sera have shown that a case of cerebro-spinal fever yields only a single " type " of meningococcus ; further, that the meningococcus which is present in the naso-pharynx of the patient at the onset of the disease is always of the same " type " as that obtained from the cerebro-spinal fluid when the latter is positive.   This we have found to be true in all cases coming under our observation.

Scott (1916) prepared monovalent sera from rabbits, and, using two cerebro-spinal and two naso-pharyngeal strains, found that cerebro-spinal strains could fairly satisfactorily be classed into two groups, but that there was a certain amount of overlapping between some of the strains. Testing 38 naso-pharyngeal strains, this observer found that 12 agglutinated most strongly with one serum, while 23 agglutinated most strongly with a second serum ; two agglutinated most strongly with a third serum, and one with a fourth.

Griffith (1916), using monovalent rabbit sera, tested 34 cerebro-spinal strains of meningococci and found that they fell into two main groups, but with a certain amount of overlapping on the part of each group ; similar results were obtained with a series of naso-pharyngeal strains.

Eastwood, Griffith and Scott, in later reports to the Local Government Board (1917), point out that the grouping of meningococci by serological methods is an artificial procedure which depends upon the arbitrary selection of particular strains as standards. Consequently, they maintain that a classification based upon

certain representatives of " types " will not answer if other examples of the same " type " are taken as the standard. Nevertheless, the practical value of Gordon's classification is undoubted and has been of the greatest service in dealing with the recent military outbreaks in this country. The agglutination test by itself, when applied in strictly quantitative fashion, has served to distinguish the true meningococci from those closely allied naso-pharyngeal organisms previously mentioned. Further, as Fildes and Baker point out, if strains are selected for standard which are really " typical " and exhibit the characters of one " type " to an almost exclusive degree, then, in spite of the occasional overlapping of " Types I. and III." and " Types II. and IV.," the difference will be sufficiently great to avoid confusion.

Using the specific " type " sera of Gordon, we investigated the agglutination reactions of 183 strains of meningococci obtained from either the cerebro-spinal fluid or the naso-pharynx. We found that 50 corresponded with " Type I.," 97 with " Type II.," 22 with " Type III." and 11 with " Type IV." The remaining three cocci (two naso-pharyngeal and one cerebro-spinal) proved inagglutinable with each of the four " type " sera, although their cultural characters and fermentation reactions were those of the meningococcus. " Type IV." cocci not infrequently gave cross-agglutination with " Type II." serum ; they did not, however, absorb " Type II." agglutinin, but always removed "Type IV." agglutinin from the homologous serum. In all cases we found that the meningococcus isolated from the naso-pharynx of an individual patient was of the same " type " as that obtained from the cerebro-spinal fluid.

Preparation of Agglutinating Serum.—The following is the method used by Gordon and Murray. A standard suspension of the coccus is made in saline as follows : A pure subculture having been obtained on a " trypagar " plate, 5 c.c. of sterile saline is poured over it and the culture emulsified. This suspension is then poured into a test-tube and heated for half an hour at 65° C. to kill the cocci and inactivate the autolysin. The heated suspension is standardised so that each c.c. contains approximately 2000 million cocci and 0·5 per cent phenol added. Standardisation of the suspension is effected by placing 0·1 c.c. in a test-tube and dropping in tap-water from a pipette until the suspension is just turbid to the naked eye when compared with a control tube of tap-water alone. This end-point is taken to represent 100 million cocci per c.c., and from this the number of cocci per c.c. of the original suspension can be calculated. The standardised phenolated

suspension can be kept in a stoppered bottle in the ice-chest and used for all agglutination and absorption tests as well as for injecting rabbits.

A standardised suspension of the particular " type " coccus having been prepared as above, young rabbits are inoculated intravenously. For rapidity of preparation Gordon and Murray used what they term a " saturation " method—$\frac{1}{2}$ c.c. of the suspension (1000 million cocci) is injected intravenously and, 48 hours later, three further $\frac{1}{2}$ c.c. doses are given at hourly intervals. By this method, within ten days, a serum has been obtained with a titre as high as 1 : 800.

Hine made a series of further experiments to determine the best method for the rapid preparation of a high-titre agglutinating serum. He found that the " saturation " method, described above, gave excellent results in some cases, but not in others. Hine finally concluded that the most satisfactory method was to inject 1000 million cocci as an initial dose, followed by 500 millions one hour later and then on the sixth day to give 3000 millions. On the eighth day the titre of the serum is estimated by withdrawing a sample of blood, and if it proves sufficiently high the rabbit is killed on the following day.

Application of the Agglutination Test in the Identification of the Meningococcus.—The method which we have adopted is that elaborated by Gordon. Four types of serum are used, each corresponding to one of the four " types " of cocci differentiated by Gordon and Murray in 1915.

A standard suspension of the coccus to be tested is prepared and inactivated as described above. The four types of serum, each in four dilutions, are placed in a series of small test-tubes ; to each tube is added an equal volume of suspension, the resulting dilutions of each serum being 1 : 50, 1 : 100, 1 : 200, and 1 : 400. A control of each type serum with its homologous coccus is put up at the same time in similar dilutions. As an additional control, the coccus under examination is also put up against normal serum in a dilution of 1 : 50. The results are read off at the end of 24 hours' incubation at 55° C.

For most practical purposes the agglutination test performed as above appears to be sufficient, but further confirmation can be obtained by means of the " absorption " test. Confusion may arise owing to the action of group-agglutinins, and also from the fact that certain Gram-negative cocci from the naso-pharynx may agglutinate with these specific sera in the lower dilutions. This, however, can be discovered by ascertaining whether or not the specific agglutinin has been absorbed from the serum. The particular sera are saturated with the suspension of the coccus to be tested for 24 hours, after which they are centrifugalised. The supernatant clear sera are then put up against their homologous cocci.

(2) *Complement Fixation.*—A number of observers have applied the complement fixation test to the identification and differentiation of the meningococcus from its allied organisms ; the results, however, have been less satisfactory than those derived from agglutination tests.

Dopter, in 1909, found that his parameningococci agreed with meningococci in fixation of complement tests.   Arkwright, in 1911, using a saline extract of the organism as antigen, tested monovalent and polyvalent anti-meningococcal sera with different strains ; he obtained positive reactions with some and negative reactions with others.   In two instances, monovalent sera tested with the homologous coccus gave a positive result.   Also, Arkwright found that meningococcal sera gave positive reactions with gonococcal as well as with meningococcal antigens.   Sophian and Neal (1911) found equally good cross-fixation between meningococcal and gonococcal sera and antigens.   McNeil, however, succeeded in preparing specific meningococcal and gonococcal antigens which gave clear reactions without any cross-fixation, and by which he was able to differentiate the meningococcus from the gonococcus.   McNeil prepared his antigen by emulsifying an 18-24 hours' growth in distilled water, heating for two hours at 56° C. and then centrifugalising for about 20 minutes.   The supernatant fluid was filtered through a medium Berkefeld filter, the filtrate being placed in sealed capsules and heated to 56° C. for half an hour on two successive days in order to ensure sterility.   Such an antigen can be kept for several months in the ice-chest ; before using, one part of 9 per cent saline is added to 9 parts of antigen.

Scott (1916) used as antigens (1) An extract of meningococcus culture and (2) Emulsions of the coccus heated to 65° C.   The second antigen proved to be the more reliable and, with its use, results were obtained which were both positive and parallel as regards specificity with those of agglutination tests.

(3) *Precipitin Reaction.*—A precipitin test for the identification of the meningococcus has been used by Dopter and others ; its value, however, is doubtful.   The test is performed as follows : An aqueous extract of the culture (autolysate) to be tested is prepared, and to 1 c.c. in a small test-tube is added 0·02-0·04 c.c. of anti-meningococcal serum ; this is then incubated for 12-24 hours at 55° C.   A positive result is indicated by the appearance of turbidity.

Toxin.—The meningococcus exerts its toxic action by means

of an intracellular toxin (endotoxin). Cultures of the organism sterilised by heat readily kill susceptible animals, whereas filtered cultures do not. The endotoxin is liberated by autolysis of the organism, as a result of the action of the intracellular enzyme.

Extraction of the Endotoxin.—Of the methods employed for obtaining a solution of the endotoxin from the meningococcus, Dopter, Flexner and others made use of the autolysin for the purpose of disintegrating the organism and liberating its endotoxin. A suspension in saline is made of a young meningococcus culture and toluol added as a disinfectant. At 37° C., the meningococci undergo autolysis, and part of the endotoxin passes into solution.

The method used by Kolle and Wassermann consisted in suspending young cultures in distilled water or decinormal soda solution, and submitting them to agitation for several days in a shaking machine. After centrifugalisation the clear supernatant fluid contains endotoxin in solution.

More recently (1918), Gordon has pointed out that neither of the above methods is entirely satisfactory, the extraction by shaking being an incomplete procedure, and the autolysate method being open to the suspicion that, during the process of autolysis, the toxin may be altered. This observer, therefore, adapted to the meningococcus Besredka's method of extracting endotoxin, the results being quite satisfactory. The procedure is as follows:

A meningococcus is selected of known serological type and of such pathogenicity that 1/10 part of an eighteen hours' slope culture on trypagar, when injected intraperitoneally into a mouse, produces death within 48 hours. Not less than fifty Petri dishes of trypagar are inoculated with this culture and incubated for 18 hours at 37° C. A suspension is then made from each plate in the usual way (p. 17). Gram-stained films are made from each tube of suspension in order to exclude contaminations. The pure suspensions are mixed and centrifugalised at top speed for an hour or more, until the bulk of the cocci have been deposited. The supernatant fluid is discarded and the sediment of cocci evacuated into a Petri dish, 5 per cent of ether is added to prevent growth of any contaminations, and the dish placed with the cover off in a desiccator, the bottom of which contains sulphuric acid. Connected with the desiccator is a manometer and also a powerful vacuum hand-pump. After receiving the dish, the desiccator is exhausted, until a minus pressure of about 70 cms. of mercury has been obtained ; the tap is then closed, the desiccator being disconnected and placed in the incubator at 37° C. overnight. Next morning the contents of the Petri dish are seen to be quite dry ; the dish is taken out, the deposits scraped off, reduced to powder in a mortar, and

examined microscopically. It is weighed and stored in a glass-stoppered bottle kept in a dry cupboard in the dark. By this method a hundred ordinary plates of meningococcus culture yield an average of 1·8 gms. of dried cocci.

To prepare a solution of the endotoxin from the dried cocci, 0·1 gm. of the latter is weighed out with an equal amount of sterilised sand in an agate mortar, the resulting mixture being thoroughly ground up, for about half an hour, until the whole has been reduced to an impalpable powder. Sterile fresh distilled water is then added drop by drop and the grinding continued for another half hour until 5 c.c. of distilled water have been added. The mixture is next poured off into a graduated centrifuge tube and the amount made up to 5 c.c., if any loss has occurred through evaporation. The tube is allowed to stand overnight in the ice-chest and, on the following morning, centrifuged at top speed until all detritus has settled to the bottom. The supernatant fluid, which appears opaque, is then decanted and forms the standard extract. If used for rabbits, 0·5 per cent of phenol is added, but if for mice intraperitoneally, it is recommended that a few drops of ether be added as a preservative.

Pathogenicity.—The meningococcus is but slightly pathogenic for the laboratory animals ordinarily in use. White mice are the most susceptible, the intraperitoneal inoculation of large doses of culture giving rise to peritonitis from which the animal usually dies ; meningococci can be demonstrated in the peritoneal exudate. Guinea-pigs and rabbits are less susceptible, and very large doses, given intraperitoneally or intravenously, are necessary to produce a fatal result. Flexner considers that the smaller-sized guinea-pigs are more susceptible than the larger, but in both guinea-pigs and rabbits the reaction to an injection of meningococci is very variable—some survive large doses, while others succumb to comparatively small doses. It has been pointed out that, in rabbits, extreme emaciation following injection is frequently a characteristic feature.

Meningitis has never been produced in any animal by the intravenous or intraperitoneal injection of meningococci. Similarly, the rubbing of culture into the nasal mucous membrane has also failed to give rise to meningitis. Inoculation of meningococci into the meninges of ordinary laboratory animals does not produce meningitis, but, in monkeys, both Flexner and Stuart McDonald have produced the condition by introducing the organisms intrathecally by means of lumbar puncture. Pathologically, the resulting meningitis was very similar to that seen in the human subject, thick exudate, containing intracellular meningococci, being found

at the base of the brain and turbid fluid in the ventricles. Often, however, the inflammation was rather more severe, death occurring in 18 to 24 hours ; these cases resembled the fulminating cases in human beings, while other cases simulated those of average severity.

OTHER MEMBERS OF THE GRAM-NEGATIVE GROUP OF COCCI

Parameningococcus.—The parameningococcus was first described in 1909 by Dopter, who found the organism in the naso-pharynx, meninges and blood of cases of cerebro-spinal meningitis.

The parameningococcus is identical with the meningococcus in its morphological characters, cultural appearance and fermentation reactions, but differs from it in its agglutination reactions. The parameningococcus agglutinates with an anti-parameningococcal serum, but fails to do so with an anti-meningococcal serum. By means of absorption tests, Dopter and Pauron separated the para-meningococcus into three groups or types. In view of the various types of meningococcus that are now known to exist, it is probable that the parameningococcus of Dopter is merely one type of the former organism. According to Flexner it appears to correspond with Gordon's Type I. meningococcus.

Gonococcus.—The gonococcus is never met with in the naso-pharynx, but, as a rarity, it might conceivably be isolated from the blood-stream.

Morphologically, the gonococcus, although not unlike the meningococcus, is somewhat smaller ; the cocci are usually arranged in pairs, resembling two kidney-beans with their flattened or slightly concave surfaces adjacent, and measure 0·6-0·8μ in size. As seen on direct microscopical examination of pus, they are usually contained within the leucocytes—a characteristic feature—and are often numerous. In cultures oval or spherical forms of varying size are met with, some being much swollen and degenerate and staining very irregularly. The organism stains readily with the basic aniline dyes and is Gram-negative.

As with the meningococcus, the conditions of growth are somewhat restricted. The gonococcus is aerobic, and special media containing serum or blood are necessary for its cultivation. The optimum temperature is 37° C., and growth will not take place at 23° C. After twenty-four hours' incubation at 37° C. the colonies appear as small semi-transparent discs varying slightly in size ;

they are of a more delicate appearance than meningococcus colonies. Later (3-4 days) the centre of each colony becomes more opaque and the margin wavy.

Of the sugars ordinarily in use the gonococcus ferments glucose only. This feature distinguishes it from the meningococcus, which ferments maltose in addition to glucose.

An anti-gonococcal serum will give well-marked agglutination with the homologous strain, but less marked with other strains. The serum will also have some effect, although very slight, on the meningococcus ; anti-meningococcal serum has a similar action on the gonococcus.

Micrococcus Flavus. — The Micrococcus flavus is frequently found in the naso-pharynx, and of all the Gram-negative cocci is the most likely to be confused with the meningococcus. This micrococcus is somewhat smaller than the meningococcus, and variation in both size and staining capacity is often seen after cultivation. The colonies are small, slightly elevated, greyish discs, with rather well-defined margins, slightly adherent to the medium, and tend to be yellowish in the centre ; the pigment, varying from canary yellow to orange, may be confined to the centre or distributed throughout the colony. Sometimes, when the colony is examined within twenty-four hours of sowing, no pigment is apparent, and it is only later that a central tinge appears. Three varieties of Micrococcus flavus have been differentiated, the differences depending chiefly upon fermentation reactions. All produce pigment in varying degree, and this capacity has led to their being termed the " Chromogenic group " of Gram-negative cocci :

M. flavus I. ferments glucose, maltose, saccharose and laevulose, and grows readily at 23° C.

M. flavus II. ferments glucose, maltose and laevulose, but more slowly than M. flavus I. It grows well on serum media, but poorly on ordinary agar, and it is unusual to obtain growth at 23° C.

M. flavus III. ferments glucose and maltose slowly. It grows well on serum media at 37° C., but growth at 23° C. is variable.

With anti-meningococcal sera the Micrococcus flavus often agglutinates in very low dilutions (1:50 and occasionally 1:100), but not in higher dilutions ; it does not, however, absorb the specific meningococcal agglutinin. Also, with normal serum, certain strains frequently show similar agglutination in low dilutions ; the meningococcus does not agglutinate with normal serum.

Micrococcus Catarrhalis.—The Micrococcus catarrhalis may be found in the naso-pharynx of healthy individuals and also in the sputum of cases of bronchitis and phthisis.

The organism is a Gram-negative diplococcus, about the same size as the meningococcus, and with flattening of the adjacent sides of each of the cocci forming a pair. The cocci are non-capsulated and may be found in tetrads or small clumps as well as in pairs ; chains, however, are never seen. It is aërobic and grows at 23° C., but not strongly. At 37° C. the Micrococcus catarrhalis grows fairly well on all the common media, but on serum media it grows rapidly. After twenty-four hours' incubation the colonies appear as raised greyish-white discs, 1-2 mm. in diameter, and slightly

TABLE I

THE DIFFERENTIAL FERMENTATION REACTIONS OF GRAM-NEGATIVE COCCI

	Glucose.	Maltose.	Saccharose.	Laevulose.
Meningococcus	+	+	–	–
Parameningococcus . . .	+	+	–	–
Gonococcus	+	–	–	–
M. flavus I.	+	+	+	+
M. flavus II.	+	+	–	+
M. flavus III. . : . .	+	+	–	–
M. catarrhalis	–	–	–	–
M. pharyngis siccus . . .	+	+	+	+

irregular in outline ; the surface is somewhat glistening, and may show yellowish specks in the centre. The colony has a somewhat firm but friable consistency. After 48 hours' incubation at 37° C. the colonies become larger, more prominent and somewhat brownish in the centre, the margins being clear but distinctly irregular and jagged.

Occasionally the Micrococcus catarrhalis forms a smooth and somewhat glistening colony, the centre of which shows a few yellowish specks, but the periphery remaining clear and the outline regular.

M. catarrhalis cultures emulsify with some difficulty in saline, quite unlike the ease with which a uniform emulsion is made from meningococcus cultures. M. catarrhalis does not ferment any of the sugars commonly in use.

Micrococcus Pharyngis Siccus. — The Micrococcus pharyngis siccus is a small Gram-negative diplococcus found occasionally in the naso-pharynx. The cocci usually show very little variation,

and, in culture, the colonies are white in colour and adhere closely to the medium ; they are firm and do not emulsify easily in saline, resembling, in this respect, the M. catarrhalis rather than the meningococcus.   The organism grows well at 23° C. and also at 37° C. ; it rapidly ferments glucose, maltose, saccharose and laevulose.

Diplococcus Mucosus Capsulatus.—This organism is a Gram-negative diplococcus which is quite unlikely to be confused with the meningococcus.   It is capsulated and grows easily at 23° C.   The colonies are large, smooth and greyish-white discs, of a mucoid or slimy consistency, which tend to become confluent.

CHAPTER III

DISSEMINATION OF THE DISEASE

Contagiousness.—A striking feature in epidemics of cerebro-spinal fever is the manner in which cases are disposed in different districts, showing little or no evidence of direct communication between those in one place and those in another, and the disease often spreading irregularly from one locality to another. Areas affected at the same time are frequently separated by districts that are practically free, and an outbreak often appears to spread from several comparatively small centres rather than from one centre of greater magnitude.

Compared with that which occurs in other epidemic diseases a relatively small portion of any community contracts cerebro-spinal fever, and statistics show that direct spread from one patient to another is unusual. Further, only a small percentage of those exposed to the risk of infection ever contract the disease. In the New York epidemic of 1893, Berg did not find among his cases a single instance of more than one member of a family developing the disease. In the 1904–5 epidemic in the same city, Bolduan and Goodwin state that of 1500 cases there were only 88 instances (5·8 per cent) of more than one case in the same house ; of these, in only 19 did more than two cases occur. During the Texas epidemic of 1912, two members of the same family were affected in 5 per cent of cases, and three members in one instance only. In the Victorian epidemic (Australia) of 1915–16, of 436 cases, there was evidence of contact with patients suffering from the disease in 21 (4·8 per cent), and in only 10 instances (2·3 per cent) were there multiple cases in the same house.

In the literature of the subject many instances of direct contagion are recorded in detail. For instance, Sewall mentions six

members of one family in New York, who contracted the disease at intervals of from 1 to 34 days. Leichtenstern (1885) reported the fact of four nurses developing the disease while attending cases in the wards of Cologne Hospital ; three of these nurses had not been out of the hospital for some time previously, and could not, therefore, have contracted the disease from outside. Elser and Huntoon also report the cases of three nurses who developed the disease while attending patients suffering from cerebro-spinal fever, and Sophian quotes the case of a New York physician who, after performing an autopsy on a person who died from meningitis, developed a fatal form of the disease. In the Meningitis Hospital at Dallas, U.S.A., during the 1912 epidemic, two " internes " and twelve nurses, exposed to cerebro-spinal fever, became affected, but all recovered. In the Victorian epidemic one doctor and six nurses attending cerebro - spinal fever cases contracted the disease ; another physician who visited a case succumbed to the malady after seven days' illness.

Flack (1916) reports five instances of direct contagion coming under his observation. One case was treated at home for 14 days before a definite diagnosis was arrived at ; on the seventh day of illness the mother, who was nursing the case, contracted the disease. The second case occurred in a hospital ward containing three other men ; five days after the case was diagnosed as one of cerebro-spinal fever one of the contacts developed the disease. The third case was also in a hospital ward before being isolated, and a few days after his removal the man in the bed opposite to that which had been occupied by the case developed cerebro-spinal fever. The fourth case was another example of a mother contracting the disease from her son, after nursing him for a few days, while the fifth was that of a man who slept in a bed next to a case of cerebro-spinal fever ; the former patient developed the disease six weeks after the removal of the latter. Sheffield Neave (1917) records an instance of three young children, living in the same tenement, all dying from a fulminating form of the disease, that is, within a day or so of the onset. He also mentions the case of a boy from a similar tenement, who died from cerebro-spinal fever after seven days' illness, while a sister suffered from only a slight attack.

The contagiousness of cerebro-spinal fever, therefore, is slight but undoubted. The cultural characteristics and viability of the meningococcus are such as render it unlikely for the disease to be spread by any means other than directly from person to person.

The meningococcus is extremely susceptible to drying, and ordinary room temperature prevents its growth; hence the dissemination of the disease by means outside the human body is very limited. The fact that the meningococcus is to be found in the naso-pharynx of patients suffering from cerebro-spinal fever indicates the most obvious source of infection.

The Meningococcus in the Naso-Pharynx of Cases of Cerebro-Spinal Fever. — Kiefer (1896), Councilman, Mallory and Wright (1898) first demonstrated that the meningococcus could be found in the naso-pharynx of patients suffering from the disease, and, as a result of repeated investigations, it is now generally accepted that the organism is present in the naso-pharynx of all cases at some period of the disease.

Lingelsheim (1906) at first found 23·12 per cent of cases yielding meningococci from the post-nasal region, but later, with improved technique, isolated the organism in 93·8 per cent. He also showed that meningococci tend rapidly to disappear from the naso-pharynx of patients, the great majority of positive results being obtained during the first ten days of illness, thus,

66·6 per cent were found positive when examined from	1st to 5th day.
24·5 ,,	,,	,,	,,	,,	6th ,, 10th ,,
11·2 ,,	,,	,,	,,	,,	11th ,, 30th ,,
4·3 ,,	,,	,,	,,	,,	after 30th ,,

Goodwin and Sholly, in the New York epidemic of 1905, isolated the meningococcus from the naso-pharynx of 54 per cent of cases during the first week of illness, 33 per cent during the second week and 6 per cent later than the second month.

Netter and Debré obtained the organism from the post-nasal region as follows :

78·5 per cent during the 1st week.
60	,,	,,	2nd ,,
50	,,	,,	3rd ,,
25	,,	,,	4th ,,
15·3	,,	later than 4th ,,

Flack (1916) found the meningococcus in the naso-pharynx of 47 cases of the 48 examined. Andrewes (1916), investigating a series of 11 cases, obtained the meningococcus by means of post-nasal swabs in all instances.

The spread of the disease irregularly over widely scattered districts during the course of an epidemic, its outbreak in areas where no cases had previously been known to have occurred, in addition

to the sporadic appearance of isolated cases, must, it is clear, be explained in some manner other than by direct exposure to cases suffering from the disease.

The Meningococcus in the Naso-Pharynx of Contacts.—In 1901, Albrecht and Ghon found the meningococcus in the naso-pharynx of a man whose child had died of meningitis. Thus, these two observers established the fact, which has been amply confirmed by later investigations, that the meningococcus may be found in the naso-pharynx of persons coming into intimate contact with those suffering from cerebro-spinal fever.

Flügge (1906) found that 70 per cent of those living in close proximity to a case of cerebro-spinal fever became " carriers " of the meningococcus in the naso-pharynx. Asterman (1906) discovered 17 carriers among 24 members of families (70 per cent), in which cases of the disease had occurred, but only 2 carriers among 51 children (4 per cent) who were remotely exposed to infection. Dieudonné (1906) found 5 carriers among 39 men (12·8 per cent) who occupied the same room in which several cases had occurred. Bruns and Hohn (1907), during a severe epidemic, found 401 carriers among 1786 contacts (22·45 per cent). Of these 1786 contacts, 609 were members of families in which cases of the disease had occurred ; among these 609 persons 224 carriers were found (36·75 per cent). Herford (1908), examining 172 persons belonging to families in which cases had developed, found 43 carriers (25 per cent). Lingelsheim (1908) detected 28 carriers among 387 close contacts (7·23 per cent) during an epidemic. Bochalli (1908) found 39 carriers among 16 soldiers (62·5 per cent) sleeping in the same room as a person suffering from the disease, and 13 carriers among 114 men of the same company (11·4 per cent), but who did not occupy the same room as the patient ; of 335 men in the same battalion, but not in the same company, Bochalli found only 5·35 per cent carriers. Black (1912) discovered that 28·3 per cent of 801 close contacts were positive. Flack (1916), examining 1629 contacts, found 139 (8·53 per cent) to be carriers.

During the first half of 1917 we examined 546 contacts and found that 56 (10·25 per cent) were carriers of the meningococcus.

From the above observations it will be seen that the relative number of carriers found among persons who have been in contact with cases of cerebro-spinal fever varies within wide limits—7 per cent to 70 per cent. In considering this divergence of figures, a number of factors have to be taken into account. Firstly, it would

be necessary to know what degree of contiguity with a patient the particular observer considers as constituting "contact." That the intimacy existing between the patient and those around him influences the number of the latter found to be carriers of the meningococcus is well illustrated by Bochalli's figures—62·5 per cent of men sleeping in the same room as the case of cerebro-spinal fever were found to be carriers, while 11·4 per cent of men belonging to the same company were positive, but only 5·35 per cent of the men of the battalion—very remote contacts—proved to be carriers.

The viability of the meningococcus is such that one may be justified, for practical purposes, in considering as " contacts " only those who come into intimate and sustained association with the patient inside a closed building. Foster and Gaskell consider as contacts " all those who are members of the same family, who have taken meals in the same room, or who have slept in the same or an adjoining room."

The hygienic surroundings are also factors of some importance. Netter and Debré found 31·39 per cent of carriers in poor families, whereas among those in comfortable surroundings only 15·38 per cent were detected. Of the carriers which we discovered among soldiers during the first half of 1917, the following table shows the percentage for each class of housing relative to the number of contacts :

Huts	.	.	.	.	.	.	16·54 per cent.
Barracks	.	.	.	.	.	.	11·76 ,,
Hospital wards	.	.	.	.	.	9·47 ,,
Billets (empty dwelling-houses)	.	.	.	6·28 ,,
Tents	.	.	.	.	.	.	0·0 ,,

The number of carriers found in hospital wards is relatively high, as frequently only the immediate contacts of the patient were examined and not the other individuals in the ward. The relation of carriers to overcrowding is well illustrated by the findings of Johnston, thus :

Conditions.	No. of Contacts.	No. of Positives.	Percentage.
Marked overcrowding . .	406	81	19·9
Moderate overcrowding . .	194	22	11·3
No overcrowding . . .	542	33	6·0

The length of time between exposure to infection and the examination of contacts has also an influence on the number of

carriers found. Of contacts examined by us not more than 48 hours after exposure, 8·2 per cent were shown to be carriers, while of those examined five days after only 4·4 per cent were positive.

Probably the most important factor in the examination of contacts is the particular individual making the investigation, especially as regards his dexterity in taking swabs from the naso-pharynx as well as the methods employed for the differentiation of the organisms. The meningococci are to be found chiefly on the upper part of the posterior pharyngeal wall (Fig. 1); in order to obtain a culture, the swab must be passed into the mouth and behind the palate and taken out again without being contaminated by the mouth secretions. For this purpose a long wire curved at one end and carrying a cotton-wool swab is most useful; such an apparatus we have used invariably and have found it quite satisfactory, giving the minimum of discomfort to the patient. The swab, having thus been taken, is planted on to a plate of suitable medium, the posterior
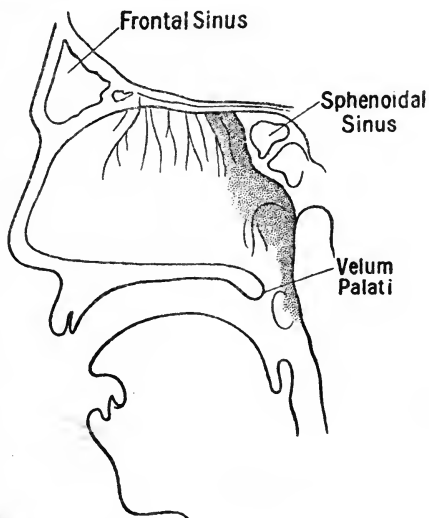
FIG. 1.—Diagram of the Naso-pharynx.
The shaded area represents the habitat of the meningococcus. (Modified from Dopter.)

part of the tip of the swab being stroked along the surface. The media employed and the confirmatory tests applied are of the greatest importance, and the more completely the latter are made use of the more the closely allied cocci can be excluded and the smaller will be the percentage of carriers found.

The number of carriers existing during an epidemic varies with the period of the outbreak, but shows a fairly definite ratio to the number of cases of cerebro-spinal fever. Several observers have demonstrated this parallel relationship between the intensity of the epidemic and the number of carriers found. Bruns and Hohn showed that the number of carriers fell from 30 per cent at the beginning of an epidemic to 5·5 per cent towards the end six months

later.   Black found that during the Dallas epidemic in 1912 the percentage of carriers became greater as the number of cases of the disease increased ; also, that during a temporary lull in the epidemic there was a diminution in the carrier rate, but that with a recrudescence of the epidemic the relative number of carriers again increased.

The Meningococcus in the Naso-Pharynx of Non-Contacts.—
Since 1901, when Albrecht and Ghon first demonstrated that the meningococcus may be present in the naso-pharynx of healthy persons, a number of similar investigations have been made on normal individuals who were not known to have been in contact with cases of cerebro-spinal fever.   Kutscher (1906), in a non-epidemic period, examined 56 non-contacts during the months of December 1905 and January 1906, and found that four were positive (7·14 per cent) ; these four persons, it is stated, had slight catarrhal affections of the upper respiratory tract.   Later, in May and June 1906—non-catarrhal period—he examined 104 non-contacts, and found that all were negative.   Kolle and Wassermann, 1906, investigated 114 people in Berlin and discovered two carriers (1·8 per cent) ; both, however, had been associated with suspicious cases of meningitis.   Droba and Kucera (1906), examining 160 children from a community free from cases of the disease, found them all negative.   Huebner and Kutscher (1907) found eight carriers among some 400 soldiers (2 per cent) when no cases were prevalent, although several months previously the regiment to which the men belonged had been stationed elsewhere in proximity to another regiment in which cerebro-spinal fever had occurred ; the eight carriers had not been in contact with each other. Schumacher and Aumann (1908) found just over 2 per cent of carriers among 1500 non-contact soldiers.   Lingelsheim (1908) failed to find any carriers among 311 individuals who were not contacts.   Lieberknecht (1909) found 8 per cent positive among 150 non-contact healthy school children.   Eastwood and Griffith (1916) detected 10·2 per cent carriers among 480 non-contact hospital patients.   Scott (1916) found 13·7 per cent positive among 138 non-contact hospital out-patients ; examining 56 healthy school children (non-contacts), he found only one suspicious positive. Flack (1916) discovered six carriers among 275 non-contacts (2·18 per cent).   Halliday Sutherland (1916) examined 100 healthy naval ratings (non-contacts), and found two positive (2 per cent). Bassett-Smith (1916) examined 4713 healthy naval ratings, who

were non-contacts, and detected 53 carriers (1·124 per cent); of these, seven were carriers of inagglutinable strains.

Early in 1917 we made an attempt to determine the " carrier rate " among healthy troops in our district, who were not known to have been in contact with cases of cerebro-spinal fever. For this purpose, naso-pharyngeal swabs were examined from 1018 men drawn from two different units—X and Y. Nineteen men were found to be carriers, that is 1·86 per cent. Of these carriers, four were found to be harbouring Type I. (Gordon) meningococcus; nine, Type II.; one, Type III.; and three, Type IV, while two carried inagglutinable strains; these latter organisms produced acid on glucose within twenty-four hours, but no change on saccharose after 96 hours. Of the X unit, 684 men were examined and 18 were found positive, yielding a carrier rate for this unit of 2·6 per cent. Of the Y unit, 334 men were examined and only one was found positive, a carrier rate of 0·3 per cent. The X men were billeted in empty dwelling-houses and the Y men were housed in barracks. The higher percentage of carriers among the X unit may be explained by the fact that the men of this unit, as a rule, are constantly moving from place to place and consequently are more liable to meet with infection. The Y men, on the other hand, usually remain in the same place for a considerable time. Further, although these men were all non-contacts, cerebro-spinal fever was more prevalent in the X unit than in the Y. In February, March and April, during which months the examinations were carried out, eight cases of cerebro-spinal fever had occurred among detachments of the X unit in different parts of the district; among men of the Y unit, however, only four cases of the disease had occurred during the month of March, and none during either February or April; it was in the latter month that the men of the Y unit were swabbed. The duration of army service of the respective men examined varied considerably; of the 684 men of X, 177 were recruits with less than eight weeks' service, the remaining 507 having served for over eight weeks. Of the 18 carriers found among these men, two had had under eight weeks' military service, 13 had served from one to two years, and three had been in the army for over two years. Of the 334 men of Y, 300 were recruits of less than eight weeks' service, and 34 had served for over eight weeks; the carrier found had been in the army five weeks. To summarise the respective periods of military service, we find three carriers among 477 recruits of under eight weeks' army service (0·629 per cent), whereas among

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540 men with more than eight weeks' service there are 16 carriers (2·78 per cent).

Temporary and Chronic Carriers.—The length of the period during which the meningococcus persists in the naso-pharynx of carriers varies within wide limits. Our experience coincides with that of Foster and Gaskell, who found that the carriers coming under their observation could be divided into two main groups, according to whether the period of carrying was short or long. In one group, Temporary carriers, the meningococcus is found at the first examination, but not on subsequent examination a week or ten days later ; following this, all swabs prove negative. It is probable that in these carriers the infection is only temporary and that the organism never obtains a proper footing in the naso-pharynx. The second group consists of prolonged or Chronic carriers. In these the meningococcus inhabits the naso-pharynx for a considerable period ; occasionally it may apparently disappear for a brief interval, but reappears later.

Mayer, Waldmann, Fürst and Gruber, examining 96 carriers, found 78 to be temporary and 12 chronic. Six belonged to what was termed a periodic class, showing alternate appearances and disappearances of the meningococci. Johnston found six carriers of 3-5 days' duration, 96 of 6-30 days and 34 of over one month. Of 140 carriers under our observation, 95 were temporary and 45 chronic. These latter harboured the meningococcus for various periods up to 80 days. Fifteen of the chronic carriers retained the organism for over a month, the remaining 30 carrying for periods varying from one week to one month.

The Spread of Infection.—From the preceding observations it is obvious that the secretions of the naso-pharynx of both cases of cerebro-spinal fever and of carriers of the meningococcus are infective, and that by such secretions the disease may be transmitted to those with whom cases or carriers are in proximity. Nevertheless, only a few of those individuals coming into contact with cases ever develop cerebro-spinal fever ; instances of such direct infection have been mentioned previously (p. 27). Many more persons, however, acquire the organism and harbour it in their naso-pharynx for a varying length of time, thus becoming " carriers," either temporary or chronic. Such individuals may develop the disease or, as more frequently occurs, transmit it to others.

It is a remarkable fact that very few known carriers ever develop cerebro-spinal fever. Of 690 carriers reported to the Medical Re-

search Committee during 1915, only two developed the disease, and one of these was doubtful. Flack, dealing with 185 carriers, found four developing the disease, while, of 485 carriers observed by Fildes and Baker, none were known to develop the disease. Of 140 carriers under our care, only one at any time exhibited symptoms suggestive of meningitis ; in this case the attack was indefinite, but may have been abortive in character.

CASE I.—A soldier, aged 20 years, was found to be a carrier of Type II. (Gordon) meningococcus on April 28. For about three weeks previously he had complained of occasional slight headache, which on May 4 suddenly became extremely severe, the change being accompanied by vomiting. He was admitted to hospital next day, where, on examination, his temperature was found to be 100·6° F. and pulse 80 per minute. He complained of severe occipital headache and pain in the back of the neck ; some cervical rigidity was apparent, it being possible to flex the head only a very short distance beyond the vertical ; also there was some rigidity of the hamstring muscles, but not quite sufficient as to amount to a really definite Kernig's sign. The pupils were somewhat dilated, but there was no evidence of involvement of the cranial nerves. All other organs appeared normal. Lumbar puncture yielded a perfectly clear fluid under considerable pressure, but proving sterile. A blood culture was also negative. On the following day the temperature had fallen to 100° F. and the symptoms had much diminished ; one day later the temperature was normal and the patient felt fairly well. A swab from the naso-pharynx on May 10 again showed the presence of Type II. meningococcus. Active treatment was then applied to the nose and throat, and subsequent swabs on May 20 and 25 proved negative.

Instances of carriers transmitting the disease to other individuals are more numerous, but absolute proof is difficult to obtain, as it is rare for a person to be proved a carrier before he is examined as a contact of a case of the disease. We have fairly conclusive evidence, however, of carrier transmission in at least one instance. A corporal, who had been stationed in Surrey for some time, obtained leave of absence to get married. He joined his fiancée on March 25, was married on the 27th, and returned to duty on the 28th. On the following day his wife was taken ill with cerebro-spinal fever and died on April 2. On April 4 a local doctor took a swab from the man's naso-pharynx ; it was examined in a London laboratory, from which it was reported as yielding meningococci. We swabbed the man on April 11 and found him to be carrying Type II. (Gordon) meningococcus. It might be suggested, of course, that the woman

had the meningococcus in her throat and infected the man ; if such were the case, it is indeed a very remarkable coincidence that she should develop the disease only after contact with her husband. The latter met the woman on March 25, and she developed the disease on the 29th, a very suggestive incubation period of not more than four days.

A soldier's child was taken ill with cerebro-spinal fever on October 25 and died on the 26th. The man had been sleeping in the same room as the child for five weeks previously and, on being swabbed immediately after the child's death, was found to be a carrier. In this case, however, one cannot exclude the possibility of the man having acquired the infection from the child. In four cases recorded by Flack the children of soldiers developed the disease soon after the arrival home on leave of the fathers, who subsequently in each case proved to be carriers. This author also quotes the case of a man confined to hospital for two months, on account of an accident, before he developed cerebro-spinal fever ; the staff nurse of the ward was found to be a chronic carrier.

The first civilian case of the outbreak of cerebro-spinal fever in England in December 1914 was that of a nurse who died twenty-four hours after the onset of the disease ; she was known frequently to have been in the company of an officer of the Canadian Expeditionary Force who, on being swabbed, proved to be a carrier (Reece). Cases of cerebro-spinal fever had occurred among the Canadian troops while in Canada, on the transports and in camp on Salisbury Plain ; the first case after their arrival in England occurred on October 18. The second civilian case was that of a child who lived at an inn frequented by Canadian soldiers ; she was attacked on December 30.

Cerebro-spinal fever appeared in Winchester early in 1915. The first case was that of a girl, aged 14, who lived in a public-house frequented by Canadian soldiers ; she was attacked on January 7. The second case was that of a boy, aged 12, who developed the disease on January 21, and whose mother had visited the first case, before and after her admission to hospital, but prior to the diagnosis of cerebro-spinal fever being made. The woman was found to be a carrier. The first military case at Winchester was that of a soldier, on duty as a guard with some Canadians. The second military case was that of a band-boy ; the members of the band were swabbed and two carriers found, one being a bugle teacher. The possibility of infection in the course of instruction immediately

suggests itself.   The nurse who attended this boy during the few hours that he was in hospital became a carrier and was rigorously isolated ; a new nurse, arriving at the hospital and not knowing the regulations concerning the isolation of the first nurse, spent an afternoon in her company and, about ten days later, developed cerebro-spinal fever and died in two days.

Sophian quotes the case of an " interne " in one of the New York hospitals who developed meningitis, although there had been no such cases in the hospital for over a year, nor had he seen any outside the hospital for some months.   A Greek immigrant, however, who had been admitted to the hospital some four or five days previously, was swabbed and found to be a carrier.   This immigrant was not suffering from meningitis, but had just come from Greece, where an epidemic was then raging.   In this connection it may here be remarked that a suspicious source of infection is not necessarily the actual one, as the following example shows.   A gunner was found to be a positive contact of one of our cases on March 5.   He was isolated and re-swabbed on March 10, with a negative result.   Nevertheless, he was placed on treatment for one day, and again swabbed on the 12th, 14th and 17th of the same month, with uniformly negative results.   He was therefore released from isolation on March 18.   The man was stationed in the neighbourhood of his home, where he was a frequent visitor, in fact, practically every evening when off duty.   His sister, who was employed daily in London but returned home each evening, contracted cerebro-spinal fever and died on April 16, after a very short illness.   Naturally the doctor in attendance suspected the soldier-brother to be the source of infection, particularly as he had previously been isolated as a carrier.   We were able, however, to reassure both the doctor and the soldier that wherever the sister had acquired the infection, she certainly did not derive it from her brother, for his naso-pharyngeal swabs, taken on April 17 and again some days later, were clearly negative.

Clinical observation, as apart from bacteriological proof, occasionally points to carrier transmission.   Steiner and Ingreham mention the case of a hospital attendant, in charge of a patient suffering from cerebro-spinal fever, who went home, with the result that four days later his own child developed the disease.   In some instances, in the course of an epidemic, a chain of intermediaries may be detected.   Steiner records the example of a woman who attended the funeral of a child dead of meningitis, consequently being in

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contact only with the relatives of the deceased.   On returning home the woman infected her own two children, who became ill four days later ; in the meantime, these two children had infected two other children with whom they played in an adjoining street.   In a series of instances recorded by Jehle, children were attacked in houses which were not connected otherwise than by the fact that the fathers worked in the same coal-pit and in the same part of the pit. Further examples will be mentioned in the section dealing with the incubation period of the disease (p. 53).

The fact that one carrier may transmit the meningococcus to another person, and so render the latter also a carrier, is borne out by the following example.   The corporal mentioned above as having infected his wife returned to his unit on March 28 and slept in the room of a billet with three other soldiers until the following day, when he was again summoned home on account of his wife's serious illness.   Of the three men who were in contact with him that single night, one became a carrier.   We had no opportunity of examining this man until twenty-four days later, when, notwithstanding this interval, we found the same type of meningococcus in his naso-pharynx as was isolated from that of the corporal.

The spread of infection, therefore, may occur by any one of the following means : from a case to an individual who develops the disease ; from a case to a person who becomes a carrier ; from a carrier to another individual who also becomes a carrier ; from a carrier to one who develops the disease.   At present, all evidence is in favour of the direct spread of the meningococcus from throat to throat.   This is brought about by the spraying of the discharges from the nose and throat, as in sneezing, coughing, speaking, etc. Colebrook and Tanner failed to obtain growths of the meningo-coccus on plates held directly under the nostrils of a carrier breath-ing heavily for several minutes.   Explosive expiration, however, gave a positive result ; sneezing and coughing on to the plates, particularly the former, also yielded cultures of the organism.

Infection may also be acquired by absolute contact, e.g. kissing ; it is possible, although very unlikely considering the cultural characters and viability of the meningococcus, that indirect spread through contaminated clothing, etc., may occur.   The presence of carriers in a community, however, fully explains the disconnected manner in which most of the cases occur, and also the distribution of the disease over widely scattered areas.   Chronic carriers are probably those most responsible for the spread of cerebro-spinal

fever ; also these carriers, as well as the occurrence of sporadic cases of the disease, serve to keep the organism alive from season to season and from one epidemic to another.

Although many individuals may run the risk of infection, comparatively few contract the disease. The majority of persons, therefore, must be relatively insusceptible to cerebro-spinal fever ; also certain conditions must appear which render individuals more susceptible at some times than at others and which favour the transference of the meningococcus from one person to another. Carriers of the organism may harbour it for many months, remaining quite healthy, and, as we have already pointed out, rarely developing the disease.

With a view of determining whether or not immunity could be demonstrated in the blood of carriers by a study of their agglutination reactions to the meningococcus, we carried out investigations on 25 proven carriers :

4 were carriers of Type   I. (Gordon) coccus.
17   ,,   ,,   ,, Type II.   ,,   ,,
3   ,,   ,,   ,, Type IV.   ,,   ,,

1 was a carrier of an inagglutinable strain, that is, a strain inagglutinable with any of Gordon's four " type " sera, but which, nevertheless, gave the sugar reactions of the meningococcus.

The serum of each was tested by the macroscopic method, and incubated for 24 hours at 55° C. in dilutions of 1 : 10 downwards. In every single case the agglutination reaction was negative. The coccus used was either the organism isolated from the individual himself or one of the same " type." Of the four carriers of Type I. coccus, three were found negative without treatment on re-swabbing 8-14 days later, while the fourth carried for seven days ; two were tested against their own organisms and two against Type I. stock cocci. Of the 17 carriers of Type II. coccus, nine were negative without treatment on re-swabbing 5-9 days later, and eight carried 7-16 days ; eight were tested against their own organisms and nine against Type II. stock cocci. Of the Type IV. carriers, two were negative without treatment 6-8 days later, but the third carried for 21 days ; the latter was tested against his own organism and the former against Type IV. stock cocci. The carrier of the inagglutinable strain was found negative on re-swabbing seven days later ; he was tested against his own organism. Therefore, as far as the

agglutination reaction of the blood serum is an index of the immunity possessed by an individual against the meningococcus, none of these 25 carriers showed evidence of any immunity.

The influence of overcrowding and unhygienic surroundings in determining the number of positive contacts is well illustrated by the figures of Netter and Debré and Johnston, previously quoted (p. 30). Of 88 positive contacts found by us in 1916–17, eleven came from overcrowded dwellings (12·5 per cent). Flack, when treating carriers, found that whatever form of treatment was adopted, a spell of sunshine markedly influenced the rate of their discharge from isolation. This suggests that fresh air tends to rid the naso-pharynx of meningococci, and so prevent the spread of infection. In a small outbreak in 1915, among troops housed in huts at Cherry Hinton, the air space was 300 cubic feet and the ventilation 2 square feet per man. Sims Woodhead improved the ventilation by knocking out a board from under the eaves all round each of the huts and no further cases occurred.

Halliday Sutherland contends that under conditions of free ventilation and fresh air it is impossible for meningococci to pass from throat to throat. His arguments regarding the mode of infection are summarised below, and his views have our entire support.

Droplets of infected naso-pharyngeal secretion float in the air according to the density and humidity of the atmosphere. Air-borne meningococcal infection can only occur in a warm atmosphere, *i.e.* at an atmospheric temperature above 71·6° F. (22° C.), the organisms dying at a lower temperature. Epidemics usually begin in January and February and disappear in May or June. January and February are the two coldest months of the year ; cold weather tends to the shutting off of the means of natural ventilation, the indoor air becoming warm and saturated and permitting the meningococcus to be carried by the air from person to person. Overcrowding predisposes to infection chiefly on account of the warm saturated air which results from it. Infection does not spread in the warm summer months because the air is less saturated with droplets of secretion, which are dried up more rapidly, the meningococcus being especially susceptible to drying.

At the present time, therefore, the bulk of evidence is in favour of spread from throat to throat inside houses, schools, theatres, etc., and wherever large numbers of people congregate together.

CHAPTER IV

PREDISPOSING CAUSES

In the present state of our knowledge of the rise and fall of epidemics, it is no easy matter satisfactorily to account for the periodical outbreaks of cerebro-spinal fever. It would appear, however, that in addition to the immediate exciting factor of the presence of a meningococcus of sufficient virulence, there must exist certain predisposing factors capable of affecting equally a considerable number of persons. With the advent of a virulent organism in a susceptible community, whose general resistance is diminished by certain predisposing agents, an epidemic of cerebro-spinal fever occurs. The probable predisposing factors will now be discussed.

Climatic Conditions.—That climate *per se* is not responsible for the presence of cerebro-spinal fever in a particular country is shown by the geographical distribution of the disease, its occurrence having been noted in almost every part of the world. Neither does there appear any direct relationship between extreme cold and outbreaks of the disease, a number of epidemics having occurred in very mild winters, while others have begun or increased with the advent of warmer weather. As instances, cerebro-spinal fever appeared in epidemic form during the mild winter of 1839–40 at Metz and in Italy, 1862–63 in Indiana and 1866 in Kentucky, while an outbreak occurred in 1868 at Smyrna during a hot spring. In England, also, the recent widespread appearance of the disease took place during the comparatively mild winter of 1914–15. A few epidemics have developed even in summer : in 1839 at Bordeaux, 1842 at Toulouse, 1850 at Dublin, and in 1874 in Galicia.

Sudden and marked variations in temperature, to which a community are unaccustomed, would appear to exert an important influence in predisposing to the disease, and would also explain its

appearance in the warmer climates. Temperate regions, in which cerebro-spinal fever is particularly prevalent, frequently exhibit, during the winter and early spring, extreme variations in the daily temperature. For the individual to adapt himself to these sudden changes is often most difficult. As Foster and Gaskell point out, the mean surface temperature of the human body varies considerably in different seasons of the year, and its process of alteration is gradual. Consequently, rapid daily variations in temperature may have a decided effect upon an individual, although he may be well accustomed to greater changes of temperature, far exceeding the daily variation in question, between the summer and winter seasons. Owing to the fact that relative to volume, children possess a larger surface area than adults, they are more susceptible to such changes.

Sophian states that prior to the last epidemic affecting the south-western States of America, the district had suffered a drought for three successive hot summers; also, for a number of years the winters had been very mild. The winter during which the epidemic occurred, however, was unusually severe and in Texas was characterised by marked variations in temperature, one day resembling mild spring and the next cold winter. Further, the advent of spring was much delayed, but with the appearance of uniformly warm weather the epidemic disappeared. Similar conditions existed in Kansas City, where there were also many cases of the disease.

In 1915–16, we attempted to ascertain the possible relationship existing between the atmospheric conditions and the case incidence of the disease. In a certain district (District A), from which we received all military cases of cerebro-spinal fever occurring therein, and where daily meteorological readings were available, the mean maximum and mean minimum temperatures per month were compared with the number of cases admitted to hospital per month. The result is illustrated in Fig. 2. It will be seen that the case incidence for District A follows the usual seasonal prevalence of the disease, reaching its maximum in April. The total number of cases (37) is not large, but since the atmospheric conditions may vary in different localities, although not widely distant from each other, it is necessary to confine investigation to one particular district. During the comparatively cold month of November 1915 no cases occurred; in February and March the temperature generally was low, and was accompanied by a slight increase in the number of cases. In December 1916, with a falling temperature, an appreciable rise occurred in the case incidence. Nevertheless,

with the appearance of slightly warmer weather during the month of April 1916 the largest number of cases was recorded. These observations, therefore, bear out the statement that there is no apparent relation between low atmospheric temperatures and cases actually suffering from the disease.

As a predisposing factor, a large amount of rainfall is of no
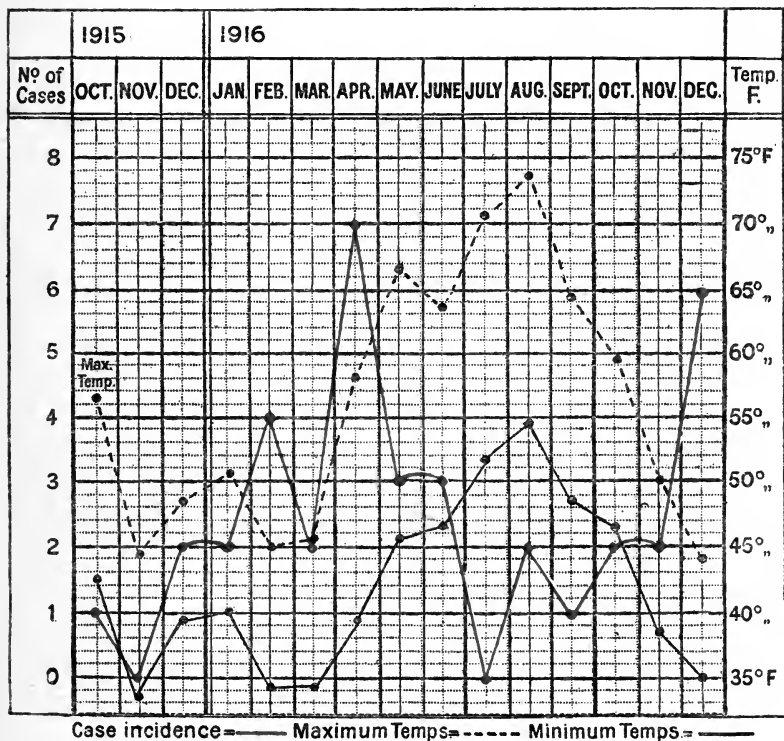
Fig. 2.—(District A.) Case incidence per month (Cerebro-spinal Fever) in relation to mean maximum and minimum temperature.

apparent importance ; on the contrary, however, there appears to be some connection between diminished rainfall and an increase in the case incidence of the disease. The autumn of 1914 was one of the wettest on record, but the epidemic of 1914–15 did not begin until late in December ; it reached its height in 1915 during April and May, which months were particularly free from rain. Fig. 3 illustrates the total amount of rainfall per month in relation to the number of cases of cerebro-spinal fever occurring in the above-

mentioned District A.   In addition to the total rainfall, the normal

FIG. 3.—(District A.)   Case incidence of Cerebro-spinal Fever in relation to rainfall (per month).

Case incidence = ━━━━━━   Total Rainfall = ━━━━━━   Normal Rainfall = ━ ━ ━ ━
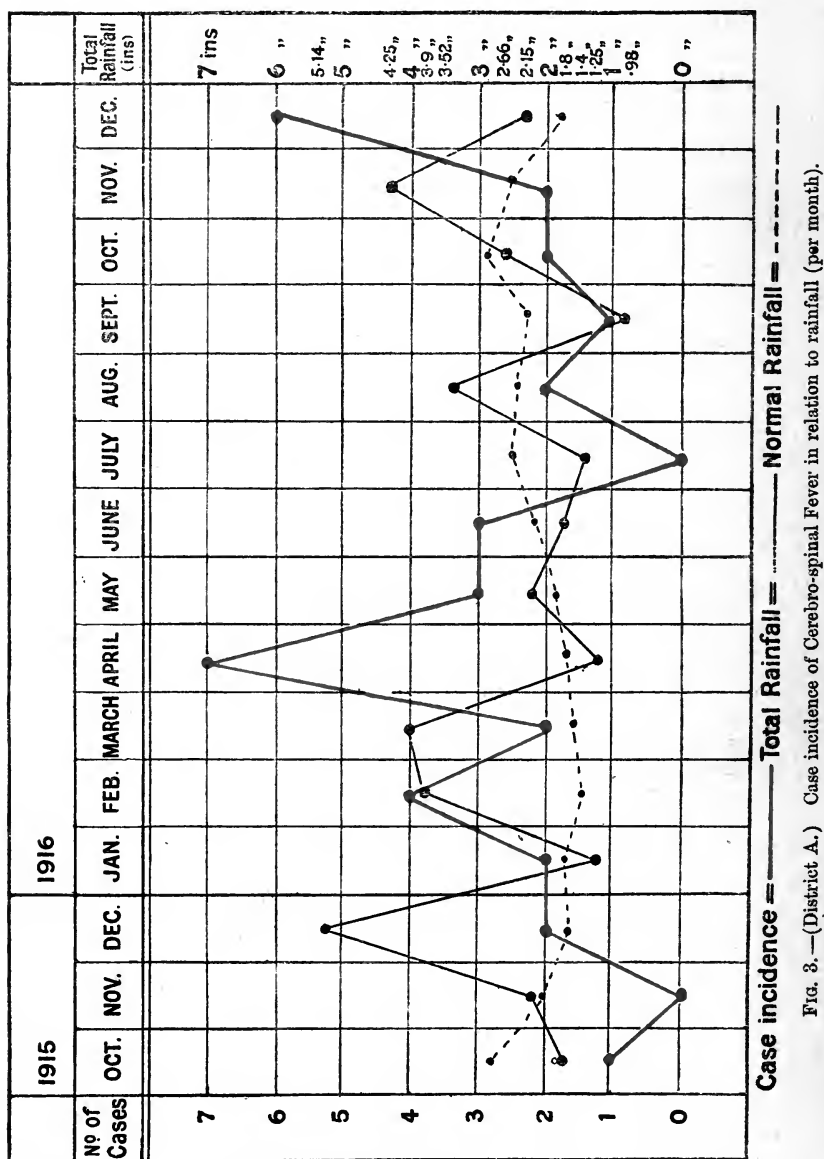
rainfall for each particular month, as estimated by Greenwich
Observatory, has also been inserted ; this latter value represents

the mean arrived at from records over a period of 65 years (1841–1905). It will be seen that the largest amount of rainfall occurred in December 1915 (5·14 ins.); this figure was considerably above the normal (1·83 in.), yet only two cases of cerebro-spinal fever appeared. This is in marked contrast with December 1916, during which six cases occurred, the rainfall (2·15 ins.) being only very slightly above normal. The total amount of rainfall for April 1915 was one of the lowest for the year (1·25 in.); nevertheless, seven cases appeared in the district; of these seven cases, five occurred after the 18th of the month, the onset of the disease in the other two taking place on the 8th and 9th respectively. There is, therefore, some apparent evidence of a relationship between diminished rainfall and an increase of the case incidence in this particular series.

During the month of December 1915 the atmosphere was generally damp, and frequent fogs occurred, more particularly towards evening. Fog, being a potent factor in producing naso-pharyngeal catarrh, which, as we shall endeavour to show later (p. 50), probably acts as a predisposing cause of the disease, may in this way play some part as an etiological factor.

General Hygiene and Overcrowding.—During epidemics occurring in cities the disease has been distinctly more prevalent among the poorer classes living in narrow streets and crowded dwellings. In the New York epidemic of 1904, for instance, 76 per cent of the patients lived in tenements where overcrowding and insanitary conditions were at their worst. Gasté, in 1840, when dealing with the military outbreak in the garrison at Metz, stated his belief that the epidemic was largely due to overcrowding of the barracks; the transferring elsewhere of some of the troops was successful in combating the outbreak. Since this time it has generally been believed that the overcrowding of barracks is largely responsible for the appearance of the disease in epidemic form among troops. Sophian points out that during 1862–63, in the United States amongst Federal soldiers at Newtown, the disease was epidemic only in those regiments which were quartered in crowded and ill-ventilated barracks.

The explanation of these facts is not far to seek. It is recognised that only a small percentage of people exposed to infection develop cerebro-spinal fever; in order to do so, however, close contact with a carrier or a case of the disease is necessary. In the poorer quarters of cities, and occasionally in barracks and billets,

this condition is adequately fulfilled. Quite as important a predisposing factor as close contact is the absence of free ventilation ; each individual in a tenement or billet may enjoy the regulation cubic content of space, but in the absence of sufficient ventilation this would speedily become inadequate. Under such conditions the mode of spread of the disease has already been described (Chap. III. pp. 34–40).

Occupation, etc.—By certain Continental writers, cerebro-spinal fever has been termed a disease of children and soldiers. Mobilised troops and children living in populous cities certainly appear particularly susceptible to infection. In the former class, the disease is considerably more frequent when the men are living in barracks, billets or hutments ; in the field it is relatively rare.

Localities in which cerebro-spinal fever appears are usually those possessing a considerable floating population ; the same statement applies to military stations and barracks. The explanation of this lies in the fact that in every community are a certain number of carriers (*vide* p. 32) ; where a population is constantly changing, there is clearly more opportunity for persons susceptible to the disease to come into contact with carriers. In New York, for instance, the various epidemics have occurred in the poorer districts, into which flows a constant stream of immigrants from all parts. Also the outbreak in England of 1914–15, as shown by Reece, was apparently introduced by the Canadian troops arriving in this country. The subsequent and widespread development of the disease is accounted for by the constant arrival and departure of large bodies of men, necessitated by the formation of new armies.

In some epidemics miners particularly have been affected ; Jehle attributes this fact to the prevalence of naso-pharyngeal catarrh among pitmen.

It is doubtful if a mere change of occupation, *e.g.* from an indoor to an outdoor life and *vice versa*, plays any part in the etiology of the disease. Of our own military cases, the patients following indoor occupations prior to enlistment and those employed in outdoor work were approximately equal in number.

Most physicians and nurses fortunately escape the disease. Several instances, however, of both physicians and nurses contracting cerebro-spinal fever while in attendance on patients suffering from the disease are on record ; some examples are mentioned in connection with infection occurring from cases (p. 27).

Fatigue.—Many observers have considered that fatigue played

some part in rendering soldiers more susceptible to the disease. Inquiry for this factor, as shown by most reports, is usually directed towards ascertaining whether or not the patient was performing some particularly arduous duty, *e.g.* a long route march, just prior to his developing the disease; such, however, is surely of less importance in diminishing resistance than the presence of *continued* fatigue, that is, the constant weariness, produced by strenuous and unaccustomed exercise day after day until trained, in the newly recruited soldier. Certain it is that in most military epidemics the maximum number of cases have occurred among recruits, *e.g.* Versailles, 1839; Strasburg, 1840; St. Etienne, 1848; Portugal, 1861–62, and New Orleans, 1874. Our own experiences have also borne this out, as illustrated by Table II.

TABLE II

SHOWING DETAILS OF THE LENGTH OF ARMY SERVICE IN A SERIES OF SEVENTY MILITARY CASES

Service.	No. of Cases.	Details of Service.	
Under 2 months . . .	38	2 weeks.	3 men
		3 ,,	14 ,,
		4 ,,	10 ,,
		5 ,,	2 ,,
		6 ,,	1 man
		7 ,,	2 men
		8 ,,	6 ,,
2-6 months	13	3 months.	6 ,,
		4 ,,	3 ,,
		5 ,,	2 ,,
		6 ,,	2 ,,
7-12 months	8	9 ,,	2 ,,
		10 ,,	3 ,,
		12 ,,	3 ,,
1-2 years	8	$1\frac{1}{2}$ years.	3 ,,
		$1\frac{3}{4}$,,	3 ,,
		2 ,,	2 ,,
Over 2 years . . .	3	$2\frac{1}{4}$,,	2 ,,
		4 ,,	1 man

An analysis of Table II. shows that over 84 per cent of the cases were men of under one year's army service. Fifty-four per cent of the patients had no more than two months' service and, of these, 71 per cent had been four weeks or less in the Army. These observations would suggest that the shorter the duration of service, the greater the liability to the disease; some allowance, however, must

be made for the fact that there are usually more recruits in home stations than men of longer service.

Previous Health and Condition.—The general physique of an individual is of little apparent importance as a predisposing cause of cerebro-spinal fever. Among military cases, we have seen the strongest of men and the debilitated alike suffer from severe forms of the disease. Further, when attacked, patients are frequently in the best of health ; in the New York epidemic of 1904 only 6 per cent of patients were reported to be in poor health when they developed cerebro-spinal fever.

In a series of 70 military cases, in which a past history was obtainable, we made careful inquiry for any previous illnesses. Of the 70 cases, no less than 40 (57 per cent) had had no previous illnesses beyond the ordinary complaints incidental to childhood ; of these 40 cases, only six proved fatal. Three further patients had had no illnesses excepting influenza or an occasional cold ; all recovered. Two patients had had tonsillitis only some years before, one had had a septic hand of moderate severity, and seven had chronic otitis media of old standing ; of these ten cases only one died.

Of the remaining 17 patients, each had had previous illnesses as follows :

Pneumonia.—Five patients had had pneumonia at periods varying from 3 to 12 years prior to developing cerebro-spinal fever ; of these, the only case which proved fatal was alcoholic.

Rheumatic Fever.—Some years previously—one case : recovered.

Diphtheria.—Twelve years previously—one case : recovered.

" *Trench Fever.*"—Nine months previously—one case : recovered.

" *Fever* " in Egypt (1915) and wounded in action three months prior to developing the disease—one case : recovered.

Chronic Nephritis.—Two cases, both proving fatal. Both patients had histories of dyspnoea on exertion ; in one case this symptom had been ascribed to a " weak heart " for two years previously. Clinically the urine showed evidence of chronic nephritis in both cases. In one case, in which autopsy was performed, early chronic nephritis was apparent, together with hypertrophy of both ventricles. A post-mortem was not performed on the second case.

Tuberculosis.—Five cases ; all died.

1. The patient complained of severe " winter cough." Clinically the lungs showed nothing more definite than somewhat impaired resonance and slightly diminished breath-sounds over the left lower lobe. Post mortem, however, old tuberculous nodules were found in both lungs, associated with pleural adhesions.

2. The patient had had frequent " colds " and a persistent cough. Tubercles were found present in the lungs at both apices.

3. Multiple tuberculous abscesses, persisting for eleven years, but finally healing six years prior to the onset of cerebro-spinal fever. This patient was of extremely poor physique and died in four days.

4. Five years previously the patient had developed a tuberculous knee ; the joint was scraped and for eight months he was unable to walk.

5. It was stated that this patient's health had always been fairly good. At autopsy, however, caseous tuberculous glands were present in the mesentery.

An examination of the above facts shows that, of the 70 patients, 53, or nearly 76 per cent, had been entirely free from ill-health, or had had previous ailments of a minor character only. Consequently it may be safely assumed that, as a general predisposing cause, the previous state of health is of no real importance.

On analysing the mortality rate in relation to previous illnesses, the following interesting facts are elicited :

Of 40 patients with a history of either no previous illnesses or those merely incidental to childhood, 6 died (mortality, 15 per cent).

Of 13 patients with a history of only minor illnesses, 1 died (mortality, 7 per cent).

Therefore, of 53 patients who had always enjoyed good health or suffered from diseases of merely a minor character, seven died, that is, 13 per cent.

Of 10 patients with previous illnesses of a moderately severe nature, 1 died (mortality, 10 per cent).

Two patients with chronic nephritis, both died (mortality, 100 per cent).

Five patients with existing or previous tuberculosis, all died (mortality, 100 per cent).

In no case that recovered was any evidence of chronic nephritis obtained. Consequently it would appear that the presence of this condition modifies the prognosis considerably. Fairley and Stewart also found that at autopsy fully 20 per cent of patients over 35 years of age presented evidence of chronic nephritis ; in those cases over this age that recovered the clinical evidence elicited pointed to healthy vasculo-renal systems.

Although, of course, it is not known to what extent tuberculous foci, healed or otherwise, but not exhibiting physical signs, prevailed

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among those patients of the above series who recovered from cerebro-spinal fever, the fact that in five fatal cases (33 per cent of the total number of fatal cases) evidence of tuberculosis was present, would certainly suggest that the tuberculous patient's chance of recovery is not of the best.   In the five cases mentioned all died from cerebro-spinal fever and not tuberculosis ; Flack, however, mentions two cases dying of acute phthisis supervening upon a moderate attack of cerebro-spinal fever ; in both cases old as well as recent tuberculous lesions were found at autopsy.

Catarrhal Conditions. — Dopter originally conceived cerebro-spinal fever as a disease falling into three definite stages—(1) Catarrhal, (2) Septicaemic and (3) Meningeal.   This view was also, in 1915, advocated by Lundie, Thomas and Fleming in England, and later by Fairley and Stewart in Australia ; the " catarrhal stage " was regarded as the most prevalent form of the disease, the meningeal stage being reached in only a comparatively small percentage of cases.   Lundie, Thomas and Fleming categorically stated that all carriers examined by them had naso-pharyngeal catarrh ; the fact, however, that such catarrh is present in all carriers has not been borne out by other observers.   The greater number of carriers that we have dealt with in the past three years have shown no naso-pharyngeal catarrh, and in the remainder the evidence that it was due to the meningococcus was most indefinite. Naso-pharyngeal catarrh, tonsillitis, etc., was present in a fair proportion of contacts found negative.   For instance, of 56 positive contacts found by us during the first half of 1917, one complained of a " cold " and " sore throat " with pharyngitis ; another had enlarged tonsils, and a third was suffering from influenza.   Among the 546 negative contacts with whom these carriers were associated, five were suffering from " colds," " sore throat," or pharyngitis, and nine had enlarged tonsils.

In the reports to the Medical Research Committee since 1915, the opinion of the majority of observers is adverse to any causal relationship between catarrh and carriers of the meningococcus. Flack, Foster and Gaskell had similar experiences to our own. When tonsillitis was present in carriers, Flack found that in the several cases investigated the condition was not meningococcal in origin.

Westenhoffer and Lingelsheim considered that a meningococcal pharyngitis occurred before the supervention of meningitis.   It is true that some cases show a varying degree of pharyngitis or other

catarrhal condition ; a fair percentage, also, complain of catarrhal symptoms, such as "sore throat," "cold" (coryza), or "cough," preceding the onset of cerebro-spinal fever. Many cases, however, show neither catarrh nor naso-pharyngitis. Even if naso-pharyngeal catarrh be present, since the majority of carriers do not exhibit this condition it is more probable that organisms other than the meningococcus are responsible for its production.

In all probability, however, a naso-pharyngitis or other catarrhal condition, by lowering the general resistance of the body, predisposes to the entry of the meningococcus into the system rather than results from its presence in the upper respiratory tract. This view, we suggest, is supported by the following observations :

(1) The greater number of proved carriers show no naso-pharyngeal catarrh ; hence the evidence that the presence of the meningococcus in the naso-pharynx produces such a catarrh is quite inconclusive.

(2) Although a catarrh of the upper respiratory tract can be demonstrated in many cases of cerebro-spinal fever, it is by no means present in all.

(3) Cerebro-spinal fever often occurs during convalescence from such catarrhal conditions as measles and influenza.

(4) An interesting table given by Halliday Sutherland, when discussing the origin and prophylaxis of the disease, shows that with an increase in the prevalence of catarrhal conditions in a barracks, cases of cerebro-spinal fever occur. The following table, modified from the above author's contribution, illustrates this :

Week ending	Total Strength of Men.	Case Incidence per 1000 of Catarrhal Conditions (Tonsillitis, "Sore Throat," and "Catarrh").
January 1 . . .	2112	7·5 ⎫
,, 8 . . .	2057	3·8 ⎪ No cases of cerebro-
,, 15 . . .	2091	6·2 ⎬ spinal fever.
,, 22 . . .	2125	13·1 ⎪
,, 29 . . .	2123	13·1 ⎭
February 2 . . .	2155	37·1 Two cases of cerebro-spinal fever

(5) In 40 per cent of our cases, a catarrhal condition was present for a period varying from four days to three weeks preceding the onset of cerebro-spinal fever. It is suggested that the onset of catarrhal condition predisposed to the attack of the latter disease.

As regards the distribution of particular catarrhal conditions

among individuals developing cerebro-spinal fever, of 70 military cases, in which a history was obtainable from either the patients themselves when sufficiently recovered, or from the close contacts, an analysis shows the following :

Twenty-one cases complained of a " sore throat " or " soreness in the throat on swallowing " ; of these, in 14 the complaint preceded the onset of cerebro-spinal fever for 3-14 days ; in addition to the " sore throat," 8 cases had complained of a " cold in the head," and 3 of a cough.

In all 14 cases, in which these catarrhal symptoms had preceded the onset, there was found, on examination, some evidence of faucial congestion, etc.

In the remaining 7 of the 21 cases, the onset of cerebro-spinal fever was accompanied by a " feeling of soreness in the throat " ; 4 of these cases had experienced a gradual onset, and 3 one of a sudden and abrupt type.

Five cases, on admission to hospital, showed congestion of the tonsils, fauces, and posterior wall of the pharynx, but had made no complaint of " sore throat."

Eleven cases had had a " cold in the head " preceding the onset of cerebro-spinal fever for 5-14 days ; in 4 of these a cough was also present.

Three cases had complained of cough only for 1-3 weeks prior to the onset of the disease. These patients usually showed some evidence of bronchial catarrh.

Traumatism.—A history of head injury immediately preceding the onset of cerebro-spinal fever is very rarely obtained. In only one case of our total series did such an incident occur. The patient was boxing when, following a comparatively slight blow on the head, he experienced violent vertical headache, and two hours later vomited. The same evening he was admitted to the local camp hospital, and regarded as a possible case of food-poisoning. Head-ache and vomiting, however, persisted, and three days later the patient came under our observation when investigation showed the case to be one of subacute cerebro-spinal fever. Eventually he made a good recovery.

CHAPTER V

INCUBATION PERIOD

In the case of most specific fevers, there is a definite interval between the time of actual infection and that of the appearance of the first symptoms of the disease. During this interval, known as the incubation period, the organism or virus, having gained access to the body, multiplies in the tissues or blood, and finally, on reaching a certain concentration, induces a reaction on the part of the body which coincides with the onset of the disease. In many of the exanthemata, the duration of the incubation period is very constant; the meningococcus, however, on gaining access to the naso-pharynx, in many instances acts merely as a saprophyte, and cerebro-spinal fever does not develop. After a period of carrying, varying from a few days to several weeks, the individual concerned usually rids himself of the organism, although, in the meantime, he may have communicated it to others. As it is somewhat uncommon for known carriers in isolation to develop the disease (*vide* p. 35), it is probable that in the majority of actual cases of cerebro-spinal fever the meningococcus gains an entry to the system very soon after the naso-pharynx is infected. This view is also borne out by certain observations on naval ratings by Fildes and Baker. Owing to certain regulations which exist in the Royal Navy, it was possible for these observers to examine naso-pharyngeal swabs from a number of men who subsequently developed the disease. For instance, in one case the naso-pharynx was negative two days before, and in two cases four days before the individuals exhibited symptoms of cerebro-spinal fever. Consequently, these observations would suggest that the incubation period is less than two days.

Further evidence available for estimating indirectly the duration of the incubation period of cerebro-spinal fever is derived from the following sources.

(1) The occasional occurrence of persons developing the disease a short time after coming into contact with a case of cerebro-spinal fever—as, for instance, in multiple family infection—or with a known or probable carrier of the meningococcus.

Examples.—A remarkable chain of infection is quoted by Netter from Richter:

R. B. spent the entire day of October 17 with a family in which there were two children suffering from meningitis. She returned home and developed the disease *four days* later (October 21). When fully convalescent 18 days later (November 8) she was visited by a young man who, in his turn, showed symptoms of meningitis *two days* after the visit; this latter patient apparently had a mild attack only, and was able to return to his office on November 15. *Four days* after his return to employment (November 19) a colleague working at the same desk developed the disease.

Incubation period: 2-4 days.

Steiner and Ingreham mention the case of a hospital attendant, in charge of a patient suffering from cerebro-spinal fever, who went home, and *four days* later his own child developed the disease in fatal form.

The following instances are recorded by Sophian:

During 1911 an epidemic of cerebro-spinal fever was raging in Greece, and among the immigrants in Greek ships arriving at New York, at that time free from an outbreak of the disease, a number of cases were occurring. A New York physician, not previously exposed to cerebro-spinal fever, performed an autopsy on one of the first Greeks dying on a steamer; *24 hours* later the physician developed a malignant form of the disease.

Another physician, treating a Greek, subsequently proved to be a carrier, for some febrile condition other than meningitis, developed cerebro-spinal fever *five days* after his attendance on this patient.

Incubation period: 24 hours (malignant) to 5 days.

Fairley and Stewart, in discussing direct infection occurring from cases, mention two examples which afford some indirect evidence of the period of incubation:

On August 7 two soldiers (J. D. and A. C.), apparently suffering from influenza, went home from camp on three days' " sick leave." Three days later (August 10) one of these soldiers (J. D.) became feverish

and developed a rash, subsequently dying from cerebro-spinal fever. His mother, who was nursing him, developed the disease on August 12, that is, *five days* after her son's arrival home.

The second soldier (A. C.) stayed until August 10 at the home of M. K. On the day of his departure (August 10—*three days* after his arrival) M. K. developed symptoms of cerebro-spinal fever. About six days later A. C. was admitted to hospital with the disease.

Incubation period : 3-5 days.

The following cases are mentioned by Reece :

In the case of a woman dying at Easthampstead on February 23 after a short illness, the cause of death was certified as " influenza ; meningitis." When she became ill, her daughter arrived from Wiltshire on February 19, bringing with her a baby aged 12 months. *Five days* later (February 24) this child was taken ill with cerebro-spinal fever (bacteriologically confirmed). Incubation period : 5 days (maximum).

At Bristol a boy aged seven years was attacked on April 20 and was removed to hospital. After an interval of *four days* (April 24) his sister became ill, and " spots " developed on her body on the following day ; this attack proved abortive, but a recrudescence occurred and she died on May 10, the meningococcus having been found. Incubation period : 4 days (minimum).

On January 30 a naval rating went home on leave from a station where several cases of cerebro-spinal fever had occurred ; he left home to return on January 31. *Five days* after his departure his sister developed cerebro-spinal fever. Incubation period : 5-6 days.

Flack, in citing instances of cases developing owing to infection by carriers, mentions the following examples :

On April 9 Sapper B. returned from France on leave ; *two days* after his arrival (April 11) one of his children was taken ill with symptoms of cerebro-spinal fever and removed to hospital. On the following day (April 12—*three days* after the father's arrival) another child developed the disease with a fatal result. The sapper was then isolated and found to be a carrier of Type II. (Gordon) meningococcus. A few days after removal the first child was discharged from hospital, the attack apparently having proved abortive ; he was brought home by his sister on a Thursday. Until then this sister had been quite well, nor subsequently did she see her father at close quarters. *Three days* after bringing her brother home (Sunday), however, she developed cerebro-spinal fever, and died within 24 hours. A naso-pharyngeal swab from the child recovering from the abortive attack yielded Type II. meningococcus. There had been no cerebro-spinal fever in the borough for the eighteen months preceding the appearance of these cases.

Incubation period : 2-3 days.

The following instance occurred in our own series :

A soldier, stationed in a district where cerebro-spinal fever was prevalent, obtained leave of absence to get married. He joined his fiancée at her home on March 25, was married on the 27th, and returned to his station on March 28.   On the following day (March 29, *four days* after his joining her, and *two days* following his departure) the wife developed cerebro-spinal fever and died within five days.   On April 4 the man's naso-pharynx was swabbed and found to contain meningococci (the type was not determined).   On April 11 a further swab yielded Type II. (Gordon) meningococci.   As stated, the man rejoined his unit on March 28 ; during the night of his return he was quartered in a room occupied by three other men with whom he had not previously been billeted.   Of the three men in contact with him for that one night, one became a carrier, and from his naso-pharynx we obtained a Type II. meningococcus also.

The above instance strongly suggests that the soldier most concerned was a carrier, and on leaving his district where cerebro-spinal fever was prevalent, infected his wife, who contracted the disease. Further evidence is offered by the fact that of three men in contact with him on his return, one became a carrier of an identical type of organism.

Incubation period : 2-4 days.

(2) In military practice the occurrence of a case among troops stationed in a district hitherto quite free from the disease, the patient having just returned from short leave in a locality where cerebro-spinal fever was prevalent.

Examples.—Three examples are mentioned by Foster and Gaskell, the cases occurring in men who had just returned from leave, and being the first instances of the disease met with at their respective stations ; consequently it is fair to assume that the disease was contracted while the men were on leave.

One man, rejoining after *four days'* leave, developed the disease on the day of his return.

A second, also having returned from *four days'* leave, developed fulminating cerebro-spinal fever on the day after his return.

In a third case the disease developed after the man's return from a period of *five days'* leave in London, where cerebro-spinal fever was then prevalent.

Incubation period : 4-5 days (maximum).

(3) Instances of an individual, after living for a considerable period in a district free from cerebro-spinal fever, or under such conditions as would render him unlikely to contract infection,

developing the disease within a short time of his arrival in a community in which the disease is prevalent.

Examples.—Gregor mentions the following example :

A man having travelled from Australia, and touching only at the Cape, developed the disease within a few days of landing at Plymouth ; it appeared, therefore, almost impossible that he should have been exposed to infection before reaching this country.

Incubation period : 3-5 days.

The following instance is cited by Foster and Gaskell :

A soldier from Bury, Lancashire, which was free from cerebro-spinal fever throughout the winter and spring, came on leave to a district in the Eastern Counties, where several cases of the disease had occurred. The man developed cerebro-spinal fever on the *third day* of his leave. These facts warrant the assumption that this soldier contracted the disease subsequent to his leaving Bury.

Incubation period : 3 days (maximum).

(4) Instances of known carriers developing the disease subsequent to their isolation for treatment. These examples are of no great value in determining the true incubation period, as the duration of " carrying " varies within very wide limits in different cases (p. 34). Further, while the organism is thus apparently saprophytic, it cannot be said to be undergoing true incubation. The most such cases show is how long may sometimes be the interval between the approximate time of primary infection and that at which the onset of the disease occurs.

Examples.—In the reports to the Medical Research Committee 1916 the following is recorded by Llewellyn :

A soldier, last in contact with a case of cerebro-spinal fever on January 28, was swabbed on February 12 and found positive. Two days later (February 14) he developed a slight headache, but on February 20 (23 days after contact and 8 days after swabbing) cerebro-spinal fever declared itself.

In the same report the following appears :

A carrier developed a fatal attack of cerebro-spinal fever more than three weeks after isolation.

Flack records the following :

A positive contact developed the disease in isolation five days after a naso-pharyngeal swab was taken.

A second carrier developed the disease seven days after isolation.

A third carrier developed the disease six weeks after isolation.

Among the contacts of one of our cases, admitted to hospital on April 27, one carrier was detected ; the coccus isolated from this carrier on April 28, however, was different in type (Type II.) from that obtained from the naso-pharynx and cerebro-spinal fluid of the patient suffering from the disease (Type I.). The carrier was placed in isolation on April 28, and six days later developed symptoms suggestive of meningitis (*vide* Case I. p. 35).

According to the above instances, carriers may develop the disease at almost any time up to six or seven weeks after infection. As pointed out above, however, such observations do not afford evidence of the duration of the true incubation period.

From a consideration of the examples yielded from the first three of the above sources, (1), (2), and (3), it would appear that the incubation period of cerebro-spinal fever varies between 24 hours and seven days, its average duration being nearly four days.

Of the reporters to the Medical Research Committee during 1915, Claridge, on studying the question in rural districts, where, as he points out, people mix less freely than in towns, found that the incubation period is usually 3-5 days, but may be 9 or 10 ; Bullock gave three cases suggesting an incubation period of four days. Fairley and Stewart, on analysing their data, were able to place an upper limit in several cases, the incubation period of which could not have been longer than five days ; in some instances the maximum duration of incubation appeared to be only three days. Other observers, no doubt arguing from instances of known carriers developing the disease, have placed a much higher figure as the maximum limit. Such cases, however, as we have pointed out, do not provide evidence of a true incubation period.

THE MODE OF INVASION BY THE MENINGOCOCCUS

It has already been pointed out (Chap. III. p. 28) that the meningococcus can be cultivated from the naso-pharynx at some stage of the disease in practically all cases of cerebro-spinal fever. Further, the organism obtained from the naso-pharynx is invariably of the same type as that isolated from the cerebro-spinal fluid ; in our experience, using Gordon's univalent " type " sera, the meningococcus cultivated from post-nasal swabs and that obtained from the cerebro-spinal fluid have answered to the agglutination and absorption tests of one and the same " type " of coccus. Consequently there can be little doubt that in cerebro-spinal fever

the naso-pharynx constitutes the portal of entry for the meningo-coccus.

There is still, however, some difference of opinion as regards the exact mode of invasion of the meninges from the naso-pharynx. The possible routes of entry to the meninges are as follows :

I. Direct Extension, *via*—

      (1) Middle ear.

      (2) Sphenoidal sinus.

      (3) Trans-ethmoidal route.

II. Indirect Route, *via* the blood stream.

I. (1) *Middle Ear.*—Infection occurring from the naso-pharynx by spreading down the Eustachian tube to the middle ear, and thence along the pia-arachnoidal sheath of the auditory nerve, has been suggested. This view, however, has no evidence in its support. Acute otitis media is most infrequent in cerebro-spinal fever and, in the comparatively rare cases in which it does occur, usually appears late in the disease. Recent otitis media was present in none of the cases under our care, although several showed chronic otitis media of old standing.

(2) *Sphenoidal Sinus.*—Investigations by Westenhoffer, Lingels-heim and E. Meyer suggested that infection might occur by direct extension from the naso-pharynx to the sphenoidal sinus ; from here suppuration would readily extend through the thin lamina of bone above the sinus. Westenhoffer found that, in 29 autopsies, 34 per cent showed some inflammation of the sphenoidal sinus ; additional support for this hypothesis was thought to be forth-coming in that in cases dying early in the disease the exudate was found localised to the base of the brain, in the region of the hypophysis. A similar localisation, however, is observed in practi-cally all forms of early meningitis, *e.g.* tuberculous meningitis, meningitis secondary to middle ear disease, etc. Also Flexner showed that there was an identical localisation in the experimental meningitis induced in monkeys by the intrathecal injection of meningococcus culture.

Westenhoffer's later observations led him to abandon his former view, as further researches failed to demonstrate either inflammatory changes or meningococci in the sphenoid bone itself, but showed that the exudate was confined to its superior and lateral aspects.

Direct extension *via* the sphenoidal sinus has again, more re-cently, been advocated by Embleton and Peters, who met with five

cases of cerebro-spinal fever in which, on post-mortem examination, the sphenoidal mucous membrane was found injected and the sinus cavity filled with pus, together with osteitis of the surrounding bone. In two cases meningococci were demonstrated in the pus cells contained both in the sphenoidal sinus and in the bone ; in one case the organism was also found in the cancellous tissue. In the other three cases meningococci were not found in the pus from the sphenoidal sinus or bone. These authors also mention a recrudescent case of cerebro-spinal fever, in which the sphenoidal sinus was opened from the nose, a drachm of pus escaping which on examination was found to contain meningococci. In 21 of Fairley and Stewart's cases, clinical investigation of the sphenoidal sinuses by Andrew failed to demonstrate any occlusion of the sphenoidal ostia. Sphenoiditis was present in four cases only ; of these, two cases showed the sinus to be acutely inflamed, the mucous membrane being thickened and covered with yellow pus. Microscopical examination of a smear, in one case, showed pneumococci. The remaining two cases had old-standing polypoid sphenoiditis.

In 28 autopsies we found nothing to support the view of direct extension *via* the sphenoidal sinus.

Although direct infection of the meninges by the meningococcus may possibly occur in rare instances, just as in pneumococcal or streptococcal meningitis secondary to foci in the nasal fossae, it is certainly not the usual mode of infection in cerebro-spinal fever. The occasional occurrence of sphenoidal sinusitis, in view of Westenhoffer's later observations, is more than probably secondary to the meningitis, rather than occupying a causal relationship to it.

(3) *Trans - ethmoidal Route.*—By experimental injections of methylene blue and chinese ink in the dog and rabbit, André demonstrated downward prolongations of the subarachnoid space, which form a network round the olfactory filaments as they pass through the cribriform plate. Other prolongations also pass through quite independently of the olfactory nerves. Further, André found that after injection the mucous membrane of the nose was coloured as far downwards as the level of the superior turbinate bone. He concluded, therefore, that by means of these prolongations a direct communication exists between the subarachnoid space and the lymphatics of the nose. The direction of the current, however, as demonstrated by these injections, is from the subarachnoid space to the nasal lymphatics. Similarly, meningococci injected intrathecally in monkeys find their way into the naso-pharynx.

As a result of the above observations Netter and Debré favoured the view that in cerebro-spinal fever direct infection occurs from the naso-pharynx through the subarachnoid prolongations described by André. It was necessary, however, in cerebro-spinal fever, to imagine a reversal of the usual direction of the current, that is, from the naso-pharynx to the subarachnoid space instead of *vice versa*. Of this assumption no definite proof exists, either experimental or pathological, and infection of the meninges in monkeys has not been produced by the inoculation of meningococci into the naso-pharynx. Neither Mackenzie and Martin nor Netter and Debré succeeded in demonstrating the meningococcus in any part of the ethmoid bone. Westenhoffer, in his fatal cases, found no evidence of extension along the lymphatics at the base of the skull and about the carotid artery, nor along the sheaths of the cranial nerves. In this connection it is of interest to note that Flexner produced poliomyelitis in monkeys by the intra-nasal injection of the virus.

The view of infection *via* the trans-ethmoidal route, therefore, although not without attraction, is somewhat conjectural ; clinical observations, moreover, as we shall show later, do not lend it much support.

II. Infection via the Blood Stream.—According to this view the meningococcus is absorbed from the naso-pharynx and carried by the blood to its site of election, the pia-arachnoid.

Cerebro-spinal fever was originally considered by Dopter as a disease falling into three definite stages : (1) Catarrhal, (2) Septi-caemic, and (3) Meningeal. This view was also, in 1915, advocated by Lundie, Thomas, and Fleming in England, and by Fairley and Stewart in Australia. According to these observers the catarrhal stage is the most prevalent form of the disease, the meningeal stage being reached in a comparatively small percentage of cases. As Horder remarks, however, this view comprises the whole series of pathogenic events open to the meningococcus, rather than connotes the disease process to which it most often gives rise. In man, for whom the meningococcus is definitely pathogenic, there is overwhelming evidence that the meninges are pre-eminently the site of election for this organism.

When discussing the probable part played by catarrhal conditions as a factor predisposing to the disease (Chap. IV. p. 51), we pointed out that not only in our own experience but also in that of many other observers the majority of carriers did not suffer from naso-pharyngeal catarrh, and in the few that did exhibit such

a condition the evidence that it was due to the meningococcus was wholly insufficient. Several reasons were also advanced for regarding catarrh of the upper respiratory passages rather as a predisposing cause of cerebro-spinal fever than a result of infection by the meningococcus.

The fact of obtaining cultures of meningococci from the blood of cerebro-spinal fever patients once definite meningeal inflammation has begun, is not, of course, proof that infection has taken place *via* the blood stream ; such a coccaemia might well have developed secondarily to the meningitis, by the escape into the circulation of meningococci from the subarachnoid space, being analogous to that which occurs at the height of meningitis induced in monkeys by the intrathecal injection of meningococcus culture. A similar possibility applies to the indirect evidence of the presence of the organisms in the blood stream, afforded by the appearance of lesions distant from the central nervous system, *e.g.* arthropathies.

Some evidence that infection takes place *via* the blood stream is furnished by clinical observations gained by a study of the onset of the disease in different cases. The onset, although occasionally preceded by a variable period of slight malaise, is usually somewhat sudden, in contrast, as pointed out by Elser and Huntoon, to that form of meningitis secondary to otitis media in which infection occurs by direct extension. In the majority of cases of cerebro-spinal fever initial rigors are present, frequent chills, and finally vomiting. Cases coming under observation at this stage (Cases II. and III. pp. 63 and 69) may exhibit pyrexia, transient erythema, and sometimes petechiae, but on lumbar puncture a perfectly clear cerebro-spinal fluid is obtained, showing no increase in its cellular constituents and devoid even of diplococci.

The most significant evidence of infection *via* the blood stream lies in the occurrence of cases of cerebro-spinal fever, in which the meningococcus can be isolated from the blood during the premeningitic stage, that is, at a time prior to the invasion of the meninges, and when meningitis can be proved, by examination of the cerebro-spinal fluid, to be non-existent. It is seldom, however, that cerebro-spinal fever is suspected in the absence of all signs of meningitis, and consequently the opportunity for taking blood cultures during such a pre-meningitic stage is missed. In the following case, which recently came under our care, the meningococcus was definitely isolated from the blood prior to the appearance of meningitis :

CASE II. **Meningococcal Septicaemia preceding Meningitis.**—
The patient, a man aged 26, had felt quite well all day, but during the
evening complained of headache.   That night he slept very little, and
next morning had several " shivering attacks," vomiting about
midday.

On admission to hospital during the afternoon he exhibited marked
pallor ; the temperature was 103·8° F. and the pulse feeble, the rate
being 120 per minute.   Beyond this there were no physical signs of
disease.

Early next morning he was found in a collapsed state, and a haemor-
rhagic rash, consisting of many petechiae and several large purpuric
spots and even patches (vibices), were seen to have appeared.   The
vibices were most numerous on and around the hips, but were also
present on the arms and legs (extensor aspects), on the abdomen, and
a few on the face.   The temperature was subnormal (96·8° F.) and the
pulse too feeble to count.   His mental condition was normal, the
sphincters were unaffected, the neck was perfectly supple, and Kernig's
sign was definitely negative.   The patient had now ceased to complain
of headache.   Lumbar puncture revealed a perfectly clear cerebro·
spinal fluid ; no increase was found in the cellular constituents and
no organisms, either on direct examination or on culture.

The patient's appearance strongly suggested that of a fulminating
case of cerebro-spinal fever, in spite of the complete absence of all signs
of meningitis.   Consequently 30 c.c. of anti-meningococcal serum
were given intramuscularly, and to keep the blood pressure as high
as possible rectal salines (6-hourly) and digitalin (gr. 1/100, 4-hourly)
were also administered.

Blood Culture.—A blood culture, taken at this time, yielded a
Gram-negative diplococcus, showing the cultural and fermentative
characteristics of the meningococcus, and, further, agglutinated by
Gordon's Type II. univalent serum.

Leucocyte Count.—This was performed the same morning, and showed
38,400 white cells per c.mm. of blood.

Blood films, taken both from the ear and from a purpuric patch,
did not show any characteristic diplococci.

Naso-pharyngeal swab yielded a meningococcus, agglutinated by the
same serum as that which agglutinated the organism obtained from
the blood (Type II., Gordon).

Meningitis.—By the evening of the same day the patient's general
condition had somewhat improved, the pulse was stronger, the rate
now being 88 per minute, and the temperature had risen to normal.
There was now some slight rigidity of the posterior cervical muscles,
and Kernig's sign appeared just positive ; the mental condition and
sphincters, however, remained normal.   Lumbar puncture yielded
45 c.c. of slightly turbid fluid, which, on microscopical examination,
showed polymorphonuclear cells and a moderate number of lympho-
cytes ; several pairs of Gram-negative diplococci were also present,

both intracellular and extracellular. The patient was given 30 c.c. of anti-meningococcal serum intrathecally.

On the following day his general condition had still further improved, although neck rigidity and Kernig's sign were more marked. The cerebro-spinal fluid remained turbid and exhibited the same cytological characters, but showed no Gram-negative diplococci.

Blood Count.—The leucocytes had fallen to 24,000 per c.mm. Serum was administered intrathecally each day until the fifth day of illness, lumbar puncture being continued until the sixth day, when the cerebro-spinal fluid was quite clear and showed no cellular increase. The patient made a good recovery.

It would appear that the above case, in the ordinary course of events, should have been of a " fulminating " type. The patient, however, came under observation very early in the disease, thus enabling therapeutic measures to be taken prior to involvement of the meninges.

Evidence of infection *via* the blood stream is also furnished by a few cases in which arthritis, apparently due to the meningococcus, has preceded the appearance of meningitis. For instance, in Saloman's case (*vide* p. 196), chills, pyrexia, and pain and swelling of certain joints occurred, meningococci being obtained on blood culture ; the symptoms persisted for two months before meningitis, also due to the meningococcus, developed. In Sophian's case (*vide* p. 196) the evidence is highly suggestive, although less definite, that meningococcal synovitis was present prior to meningitis.

A factor of great importance in support of infection *via* the blood stream is that the earliest meningeal exudate, as demonstrated by Busse and others, appears simultaneously at the base of the brain and in the meninges of the spinal cord.

It is true that experimental blood inoculation in animals has failed to produce meningitis, but the explanation of this failure may lie in the fact that all laboratory animals, as regards specific lesions, are relatively insusceptible to the meningococcus ; even in monkeys Flexner had to inject meningococci directly into the subarachnoid space in order to induce meningitis.

In some cases of cerebro-spinal fever, as illustrated by the cases above, the meningococcus may definitely infect the blood, multiplying therein and causing a true septicaemia ; thus the organism may remain confined to the blood stream for some considerable time before the meninges become involved. If the meningococcus were not primarily absorbed into the circulation, it is difficult to understand how this could possibly occur.

In many cases of the "fulminating" type death appears to result from the overwhelming intensity of the blood infection, the meningitis, as shown by post-mortem examination, being comparatively slight. In such cases, therefore, blood cultures should be positive, and this is usually found to be the case (*vide* p. 139). Occasionally, indeed, Gram-negative diplococci may be found in blood films taken from patients exhibiting a purpuric eruption; A. C. Coles, for instance, figures such films obtained from the ear of a patient who died within 50 hours of the onset of the disease.

Other examples of meningococcal infection occasionally occur, in which the meningococcus remains confined to the blood stream and never settles in the meninges; these cases are admittedly rare. In 1906 Andrewes reported a case with a purpuric eruption, and which yielded meningococci upon blood culture. The patient died in a few days without developing meningitis, evidence of which was also absent at the post-mortem examination. Pybus (1917) reported the case of a girl, aged three years, exhibiting petechiae and some small haemorrhagic patches on the lower extremities, who died within 12 hours of an acute onset. Post-mortem cultures made from the heart blood yielded a pure growth of meningococci, but the brain and spinal cord presented no signs of meningitis. More recently Herringham and others have placed on record at least three definite cases of meningococcal septicaemia. Full reference has been made to this condition in Chapter XIV. (p. 344).

It is possible, of course, that if the above cases had not succumbed to the intensity of the blood infection, the meninges might have become involved later. This assumption is justified by the fact that cases almost intermediate in character between the pure septicaemic variety and the ordinary fulminating type with meningitis are occasionally met with. In these cases the course lasts only from 24 to 48 hours; blood cultures or cultivations from the heart blood taken post mortem yield meningococci. The brain and spinal cord may be practically normal in appearance, or the ventricles may contain a small quantity of turbid fluid. The ventricular fluid, however, when planted out on to a suitable medium, gives a growth of meningococci. Such cases have been reported by Herringham and Thornley and Symmers; they are more fully dealt with in the description of the fulminating type of the disease (*vide* Chap. VII. p. 135).

In a few rare instances the meningococcus, on gaining an entry

to the circulation, may involve structures other than the meninges, the latter remaining entirely unaffected throughout the course of illness. This occurrence is well illustrated by one of our cases (Case LIX. p. 347), in which meningococcal septicaemia was present with ulcerative endocarditis. The condition ran a course of over six weeks' duration, yet no signs of meningitis were present at any stage of the disease. Two cultivations of the blood, the second being taken after an interval of nearly two weeks, yielded meningococci on each occasion, the organism corresponding to Gordon's Type II. coccus. On post-mortem examination, meningitis was found to be absent, and sections prepared from the vegetations and cusp of the aortic valve showed the presence of large numbers of cocci, exhibiting the morphological appearance and staining reactions of the meningococcus. A somewhat similar case, dying after a course of ten days, was reported by Cecil and Soper in 1911 (p. 352).

Occasionally a joint may be involved, also in the absence of meningitis. This occurred in a case mentioned by Flack (vide p. 352); the fact that a blood culture, taken on the day after the arthropathy appeared, proved negative does not exclude the probability that infection occurred via the blood stream, as the organism, on settling in the joint, would have ceased to be present in the circulation. Similarly, in most cases of cerebro-spinal fever, once meningitis has developed, blood cultures are usually negative.

In the majority of cases of cerebro-spinal fever, it is probable that the meningococcus, on reaching the blood stream from the naso-pharynx, is quickly carried to the meninges (in a few to 48 hours), constituting at this stage a coccaemia or temporary presence of meningococci in the circulation, whilst being carried to their destination, rather than a definite septicaemia in which the organisms are multiplying in the blood stream. Some recent experiments by Cresswell Shearer and Warren Crowe suggest that conveyance of the meningococcus from the naso-pharynx to the meninges may be performed by the leucocytes. These observers, using freshly drawn spinal fluid from cerebro-spinal fever patients and in which the leucocytes had been shown to be alive by trypan-blue staining and observation on the warm stage, obtained good evidence that the meningococci could be taken up in large numbers by human leuco-cytes and retained for some considerable time without undergoing digestion. The organisms could be recovered from the leucocytes up to 48 and even 60 hours.

To summarise :

1. The mode of entry by the meningococcus is almost certainly by the blood stream.

2. In the ordinary type of case the coccus is carried to the meninges by the blood within a few hours, without definitely infecting the blood itself in the sense of causing a true septicaemia.

3. In some cases definite blood infection occurs (true septicaemia), *e.g.* in most fulminating cases, prior to the involvement of the meninges ; in such cases the septicaemia often overshadows the meningitis, which may be comparatively slight.

4. In rare cases the organism may remain infecting the blood alone for a considerable period before finally reaching the meninges, or the patient may die from such septicaemia before meningitis occurs.

5. In other instances the meningococcus infecting the blood may invade structures other than the meninges, *e.g.* the cardiac valves or various joints.

CHAPTER VI

THE symptoms of cerebro-spinal fever may primarily be considered under two headings, constituting consecutive stages of the disease :

I. Symptoms at onset.
II. Symptoms subsequent to onset.

SYMPTOMS AT ONSET

The onset of cerebro-spinal fever is usually sudden and abrupt, less often gradual and more insidious ; in some cases the actual onset, though sudden, may be preceded by a period of malaise of variable duration. The types of onset, therefore, may be classified as follows :

A. **Onset Sudden.**—(1) The patient previously in good health.

(2) Preceded by a period of malaise varying from a few days to three weeks in duration.

B. **Onset Gradual.**—Three, four, or more days elapse before the meningeal symptoms are at all pronounced.

A. **Onset Sudden.**—Of 70 cases, in whom it was possible to obtain a definite history of onset either from the patients themselves when sufficiently recovered or, in those cases proving fatal, from the relatives or men sharing the same quarters, this type of onset occurred in 50 (71·4 per cent).

The onset is acute, the patient complaining of sudden chilliness or shivering ; definite rigors frequently occur. These symptoms are rapidly succeeded by severe and throbbing headache, either frontal or vertical, which soon increases in intensity ; more rarely the headache is referred to the occiput. In some instances it may accompany or even precede the initial chill. There is usually complete loss of appetite, and a few hours later the patient vomits.

The vomiting is explosive in character, is often repeated, and frequently nausea is absent. In the majority of cases, the vomiting is limited to one or two attacks, although in a few it may continue for about 48 hours. Occasionally (3 per cent of our series), diarrhoea accompanies the vomiting, being more often met with in children than in adults.

A patient coming under observation at this stage may not appear seriously ill. The mind is perfectly clear although the temperature may be high (102°-104° F.). The pulse rate is somewhat frequent but often not increased to the extent that might be expected from the degree of pyrexia present (104-116 per minute). Following the appearance of definite meningitis, the pulse rate falls to 70-90. The cervical muscles as a rule show no definite stiffness, but, as the symptoms develop, some rigidity appears; for several hours, however, it may be extremely slight. Photophobia is sometimes present, but in our experience is not common. According to Sophian, tenderness at the angles of the jaw may be marked. The patient usually appears somewhat pallid, but instability of the vasomotor system is almost invariable and *tache cérébrale* can readily be produced; at a later stage flushing occurs. Finally, an erythematous or petechial rash may develop shortly after the onset.

The following example illustrates a patient coming under observation during the above stage (pre-meningitic stage), about 5 to 6 hours after the actual onset.

CASE III.—A patient, aged 25 years, was admitted to hospital with the following history. He had felt quite well on the previous day, but this morning had awakened with headache and a " sore feeling " in the throat. A short time afterwards he experienced what he described as a " shivering attack," the headache increased in severity, and a few hours later he vomited. During the afternoon he was sent to hospital as a case of influenza.

On admission, the patient's temperature was 104° F., pulse 100, and respirations 24 per minute. His mental condition was quite normal and the sphincters unaffected; on careful examination, there appeared to be a suspicion of rigidity in the cervical muscles, the chin on passive flexion of the head just failing to reach the chest. Kernig's sign was negative; there was, however, some slight rigidity of the hamstring muscles, being more apparent on the right side than on the left. The throat appeared normal and no other physical signs were discovered. Lumbar puncture yielded 35 c.c. of perfectly clear fluid, which, on microscopical examination, showed no increase in the cellular constituents and no organisms; also, the media on which the fluid was sown remained sterile.

During the night, violent delirium developed, the temperature meanwhile having fallen to 98° F. and the pulse to 80. Early next morning all the signs of meningitis were well marked, and on lumbar puncture 50 c.c. of turbid fluid was obtained ; stained films showed many meningococci both intracellular and extracellular.

Case II., fully described on p. 63 (Chapter V.), is another example of a patient seen during the pre-meningitic stage ; the onset had occurred with headache, shivering and vomiting ; later, a purpuric eruption appeared. Blood cultures, taken at this time, yielded meningococci, the cerebro-spinal fluid being clear and showing no organisms. About ten hours later, signs of meningitis were apparent, and a turbid fluid containing meningococci was obtained on lumbar puncture.

During the pre-meningitic stage, lumbar puncture will frequently reveal an increase in both the pressure and the quantity obtainable of the cerebro-spinal fluid. It will be clear to the naked eye, and on examination show no lymphocytes beyond the normal number present ; although absent in the above two cases, a few diplococci may occasionally be seen in stained films of the centrifugalised deposit. For example, meningococci were easily visible on microscopical examination in the clear fluid of cases coming under our observation at a stage slightly more advanced than in Cases II. and III.

The initial meningeal symptoms, which appear from within a few to twenty-four hours, and occasionally longer, after the general onset, appear to be due to a rise in intracranial pressure consequent upon an increase in the total quantity of cerebro-spinal fluid contained in the subarachnoid space. This increase, in turn, is due to augmented secretion from the choroid plexuses, and constitutes the first stage of the reaction produced by the arrival of diplococci in the pia-arachnoid. The cerebro-spinal fluid may still remain clear to the naked eye, as in the following case :

Case IV.—A girl, aged 13 years, was sent into hospital with the history that on the previous day she had complained of severe headache and prostration ; during the evening vomiting occurred, and the patient appeared very drowsy.

On admission, the temperature was 101° F. and the pulse 90. A petechial rash was present over the back and arms. She was somewhat stuporose, but on being roused answered questions slowly and drowsily ; there was distinct rigidity of the neck muscles and Kernig's sign was just positive. Lumbar puncture yielded 60 c.c. of clear cerebro-spinal fluid under increased pressure. On microscopical examination no

cells were seen, but numerous Gram-negative diplococci were found ; in culture, a growth of meningococci was obtained.

A variable time after the occurrence of vomiting, delirium as a rule makes its appearance in adult cases. In those exhibiting a sudden and abrupt onset, this period, following the vomiting, varies from a few to thirty-six hours ; it is usually present by the second day, although in very mild cases it may remain altogether absent. The stage at which the majority of patients first come under observation in hospital is that of delirium.

The onset in the fulminating type of cerebro-spinal fever is often very sudden ; vomiting may be entirely absent and coma occur within a few hours of the appearance of the first symptoms. Some patients, indeed, may pass into coma without any warning symptoms. One of Foster and Gaskell's cases was found dead in bed ; another patient who recovered, had gone to bed apparently in his usual health, but at 2 A.M. was found unconscious ; afterwards, he remembered nothing of the period between his going to bed on the night of his attack and the fifth day of illness. The following examples from our own series of cases also illustrate the onset in fulminating cases :

A soldier, aged 19, had felt quite well during the whole morning and attended the riding school until 12.30 P.M. At 2 P.M., however, he felt too unwell to return, complaining of headache and lassitude. At 6 P.M. he was found unconscious in his hut, and died within 36 hours.

A rifleman, aged 18, had a hearty meal of cakes at 4 P.M. A few hours later he complained of headache and vomited. During the night he became delirious and died next afternoon.

In other cases, apart from those of a fulminating type, the onset may sometimes occur with startling suddenness, thus :

A soldier, aged 28, feeling quite well, reported one afternoon for anti-typhoid inoculation. Whilst waiting with other men he complained of headache ; this rapidly became so severe that in a few minutes he was unable to stand. An hour or so later he had several rigors followed by vomiting.

A driver, aged 20, went to bed one evening in his usual health ; in the morning he was found delirious and violent.

In infants and young children the disease may begin as abruptly as in the adult ; it is often ushered in by a convulsion, which may be repeated during the process of meningeal involvement. Vomiting occurs less frequently than in the adult, but diarrhoea may be

present. Hyperaesthesia is an early and prominent symptom, the child crying or screaming on being moved. Goeppert states that he was enabled to make an early diagnosis in several cases by this symptom alone ; unfortunately, however, it is seldom that children come under observation before the ordinary signs are well marked. Bulging of the anterior fontanelle may occur at a relatively early stage, owing to the increased quantity of cerebro-spinal fluid prior to definite inflammatory changes.

(1) *Onset sudden, the patient previously being in good health.*—Of 50 cases in which the onset was sudden and abrupt, 28 (56 per cent) of the patients were in apparent normal health at the time of their developing the disease ; 13 recovered and 15 died (mortality 53·6 per cent). Five of the cases were of a fulminating type. Vomiting occurred in all excepting three ; of these, two were fulminating cases becoming comatose within a few hours of the onset and each dying after a course of less than 36 hours. Excluding the five fulminating cases and one infant, 19 of the remaining 22 became delirious within 8 to 36 hours of the onset. In one of the cases in which delirium did not occur at an early stage, the primary onset, though sudden and abrupt, led up to only an abortive attack of the disease ; this, after a few days' interval, was followed by a recrudescence in the form of a more definite attack, and in which delirium was a prominent symptom (Case XXI. p. 162).

(2) *Onset sudden but preceded by a period of malaise.*—This condition occurred in 22 (44 per cent) of the 50 cases exhibiting a sudden onset. In the majority, the " malaise " consists of a catarrhal condition, such as " sore throat," " cold in the head," or " cough," which, as suggested elsewhere (p. 51), probably predisposes to cerebro-spinal fever ; the duration of these symptoms varies from four days to three weeks. The actual onset differs in no way from that described in the preceding section ; the catarrhal symptoms quite suddenly change to acute headache, shivering, and later, vomiting. Illustrations are seen in the following examples :

A soldier, aged 21, had had a "cold " for about a week, with occasional slight headache ; it was insufficient, however, to cause him to " report sick." One evening, following this, he was seized with violent headache, and about midnight shivered violently. The headache continued, a few hours later he vomited, and next day became delirious.

A man, aged 32, had had a severe cough for ten days. One morning he complained of headache and pain in the limbs ; three hours later he vomited and was delirious by evening.

Cerebro-spinal fever may follow measles or influenza, as in the following cases :

A man, aged 27, was almost convalescent from rubella ; the cough, however, had not quite disappeared. He had a definite rigor followed by headache, and developed typical cerebro-spinal fever.

A youth, having recovered from a comparatively mild attack of influenza, had been up for only three days, when, on the following morning, he complained of headache and would take no breakfast. During the afternoon he vomited, and was delirious by evening.

Loss of consciousness may occur somewhat suddenly, as with patients previously in good health, thus :

A soldier had had a cough and " sore throat " for about a week ; he was waiting to " report sick " one morning, having vomited an hour before, when, on his name being called, he was found to be quite unconscious.

A gunner, aged 22, had had a " cold " and " sore throat " for about four days. He paraded as usual one morning not appearing any worse ; later, however, it was noticed that he did not eat any dinner. About half an hour later, he attended " roll-call," and whilst waiting, fell down and was picked up unconscious.

Of the 22 patients in this category, 15 recovered and seven died (mortality 31·8 per cent). Vomiting occurred in all excepting three, while delirium or unconsciousness supervened in 17.

B. **Onset Gradual.**—A gradual onset occurred in 20 of the 70 cases analysed (28·6 per cent). It consists of gradually increasing headache and pain and stiffness in the limbs ; backache may also be complained of, and sooner or later the patient usually vomits, although this symptom may be delayed for three or four days. Sleeplessness and loss of appetite are well-marked features, and may be accompanied by a feeling of soreness in the throat and, occasionally, epistaxis. Abdominal pain is not infrequent, and diarrhoea may also occur. Such symptoms may be present for three days to a week before the patient is compelled to remain in bed, or finally arrives in hospital ; in the latter case, it is almost invariably with a diagnosis of influenza or gastritis.

Catarrhal conditions (" sore throat," coryza, and " cough ") may sometimes accompany or, in some cases, precede for a few days this type of onset. In contrast, however, to those cases exhibiting a sudden onset following a period of malaise, one is unable to trace any appreciable division between the catarrhal symptoms and those

of the onset of cerebro-spinal fever. The following examples illustrate a gradual onset :

A private, aged 25, having felt " out of sorts " for three or four days, complained of gradually increasing headache for about a week. During this period, he had vomited occasionally and suffered also from loss of appetite and general weakness. He had been told by men sleeping in the same hut that he continually shouted in his sleep. On arrival in hospital as a case of influenza, he was found to be suffering from subacute cerebro-spinal fever.

A lorry-driver, aged 19, " reported sick " with headache and " pain all over." This complaint persisted, and three days later he vomited. Epistaxis occurred on the following day, but four more days elapsed before severe headache and muscular stiffness appeared.

A bugler, aged 15, having felt " chilly " for two days, complained of headache and abdominal pain ; these symptoms remained, and on the following day he vomited. He did not remain in bed, however, until next day, when the headache was considerably more severe ; on his being transferred to hospital cerebro-spinal fever was diagnosed.

Cases developing insidiously are frequently subacute and give rise to errors of diagnosis because cerebro-spinal fever is entirely unsuspected, owing no doubt to the normal consciousness and atypical appearance. We have known such a patient, at first regarded as suffering from influenza, arrive in hospital smoking a cigarette. Careful examination, however, will invariably reveal the muscular rigidities indicative of meningitis.

Of the 20 cases exhibiting a gradual onset, 16 had vomited before being admitted to hospital. Delirium eventually appeared at some time during the subsequent course in 14 cases of the 20 ; in some it was merely nocturnal and continued for only a day or two. For the most part the cases were but mild or moderate examples of the disease, three only proving fatal (15 per cent).

SYMPTOMS SUBSEQUENT TO THE ONSET

Following the onset of the disease, the subsequent symptoms may be regarded as falling into two separate groups : firstly, those due to an acute specific fever, and secondly, those arising from the involvement of the central nervous system, around which the chief infection becomes localised. Certain symptoms, *e.g.* headache, are produced by both factors in common ; such, therefore, together with those referable to the acute general infection, will be considered before those due to involvement of the central nervous system, and under the following heading.

General Symptoms

Headache. — This is a constant symptom, often of great severity at the onset, and occurring with varying intensity throughout the course of illness. The headache usually appears to be more or less general, although in some cases it may be chiefly frontal or vertical ; more rarely it is referred to the occipital region. Occasionally this symptom may be so severe as to cause the patient to scream with pain ; not infrequently it is associated with pain at the nape of the neck. Headache does not cease when the patient becomes delirious, in fact, it is often the subject of his delirium. In cases developing internal hydrocephalus, headache is particularly complained of, being one of the earliest symptoms of this grave complication. With improvement in cases recovering, the headache gradually disappears.

As with the other specific fevers, the primary headache is the result of the initial infection ; later it is probably due to the increase in the quantity of cerebro-spinal fluid, which, in turn, causes a rise of intracranial pressure, thereby producing a disturbance of the cerebral circulation. This view is borne out by the fact that the headache is frequently relieved by lumbar puncture.

Catarrhal Symptoms. — In the section dealing with the predisposing causes of the disease it was pointed out that in some cases (40 per cent) catarrhal conditions, such as " sore throat," coryza, or " cough," may precede the onset for a period varying from a few days to a few weeks ; these ailments, it was considered, may in some measure predispose to cerebro-spinal fever (*vide* Chapter IV. p. 41).

The bronchial catarrh occasionally present at the onset of cerebro-spinal fever may later lead to bronchitis or broncho-pneumonia. Of four cases who had complained of " cough " preceding the onset of the disease, two developed bronchitis and two broncho-pneumonia. Another patient, who contracted cerebro-spinal fever almost immediately following his recovery from an attack of acute bronchitis, also developed broncho-pneumonia. These conditions, however, are considered among the complications of the disease (Chapter VIII. p. 178).

A cough, with mucoid expectoration and due to a bronchial catarrh, may also occur during the course of the disease, without, however, giving rise to any definite physical signs in the chest. Many acute cases proving fatal within 5 to 7 days, show, during the

coma that precedes death a fœtid purulent discharge from the nose and throat.

Gastro-intestinal Symptoms.—*Tongue.*—Early in the disease the tongue is moist and shows a whitish fur of fairly uniform distribution ; later, the tongue becomes dry and brown, the coating often being very thick.

Vomiting.—With the onset of the disease, vomiting usually occurs ; in our series it was present in 86 per cent of all cases. The symptom is frequently absent in fulminating cases, and occasionally in the subacute form of the disease exhibiting a gradual onset. The vomiting is not as a rule preceded by nausea ; in character it is somewhat explosive, and its time of appearance varies from a few hours to three or four days after the commencement of headache. Usually the vomiting is limited to one or two attacks, but in a few instances it may continue for two or even three days. In infants, this symptom is rather less frequent than in older children and adults.

During the course of the disease, vomiting is chiefly met with in those cases running a long course and developing or showing a tendency towards hydrocephalus. As the degree of hydrocephalus increases, the vomiting becomes projectile and may be extremely difficult to control ; the patient may vomit several times during the day, the vomited matter containing well-digested food. Frequently, the symptom appears to have but little effect upon the patient's appetite.

Persistent vomiting, unrelieved by lumbar puncture, is usually an ominous sign. In one subacute case dying of internal hydrocephalus on the 54th day of illness, vomiting started on the 35th day, and with the exception of only three days, the 41st, 46th, and 49th, continued daily until death. Lumbar puncture had little or no effect, the vomiting often persisting even after the withdrawal of 30 to 40 c.c. of cerebro-spinal fluid. In the posterior basic type of infants (p. 173), vomiting is a constant symptom.

Coincident with the sudden rises of temperature following apyrexial periods, as seen in recrudescent cases (*vide* p. 161), vomiting may also occur ; this was well shown in one case of our series, that of a boy aged 15 years, whose course of illness continued for nearly twelve weeks. This patient vomited with almost every recrudescent attack of pyrexia, of which there were several.

Should pneumonia complicate the disease, vomiting may occur both at its onset and during its course.

Constipation.—As with other febrile illnesses, constipation is the general rule throughout the course. Often it is sufficiently obstinate to necessitate the use of purgatives and enemata.

Diarrhoea.—Diarrhoea occasionally occurs at the onset, being rather more frequent in children than in adults. In one of our patients, aged 26 years, diarrhoea followed the usual initial vomiting, while in another patient, aged 18 years, it occurred on the second day of illness. Diarrhoea was also present at the onset in two infants.

During the course, diarrhoea may occur in infants and young children, but in adults it is rare. In cases of over 15 years of age, we met with diarrhoea in one patient only. This patient, aged 25 years, suffered from a very acute form of the disease. On the tenth day of illness, diarrhoea suddenly replaced the previous constipation, its appearance coinciding with the termination of a hyperpyrexial period which had commenced on the fifth day. The diarrhoea ceased after lasting four days (Case VI. p. 84).

Diarrhoea may also occur, occasionally, as a manifestation of " serum disease " in cases treated with anti-meningococcal serum. In one of our cases, diarrhoea of about 36 hours' duration followed almost immediately upon the appearance of a serum rash on the tenth day of illness ; the patient had recovered on the previous day, the cerebro-spinal fluid being perfectly clear and normal (*vide* Serum Disease, p. 465). Such diarrhoea, occurring while the patient was still suffering from meningitis, might easily be misinterpreted.

Abdominal Pain.—Pain in the abdomen may be complained of at the onset of the disease or early in the course. Of 65 cases over 14 years of age, this symptom occurred in four (6·15 per cent). It preceded the initial vomiting in one fulminating case that died within 48 hours of the onset. In a second case, the abdominal pain was sufficiently severe as to lead to a diagnosis of appendicitis prior to the patient's being received into hospital. A gradual onset, accompanied by abdominal pain, is illustrated on p. 74. In infancy, the disease may begin with abdominal pain associated with diarrhoea.

Temperature.—In few diseases is the temperature more variable and of smaller value as an index to the severity of the case than in cerebro-spinal fever. At the actual onset, it is probable that a fall in temperature to subnormal occurs, coinciding with the initial chill ; following this, however, the rise in temperature is usually rapid. We were able to note a primary fall to subnormal in two

of our cases, both of whom were under observation at the time of onset.

CASE V. (illustrated by Fig. 4).—A patient, aged 18 years, of poor physique, was admitted to a general ward of the hospital on January 26th, suffering from acute bronchitis. The history given was that he had had a severe cough for about a week; on admission, the temperature was 101° F., pulse 92, and respirations 28 per minute. He had a loose cough with some mucous expectoration, and, on examination,

Date	26	27	28	29	30	31	1	2	3	4
Day of Dis.					1	2	3	4	5	6
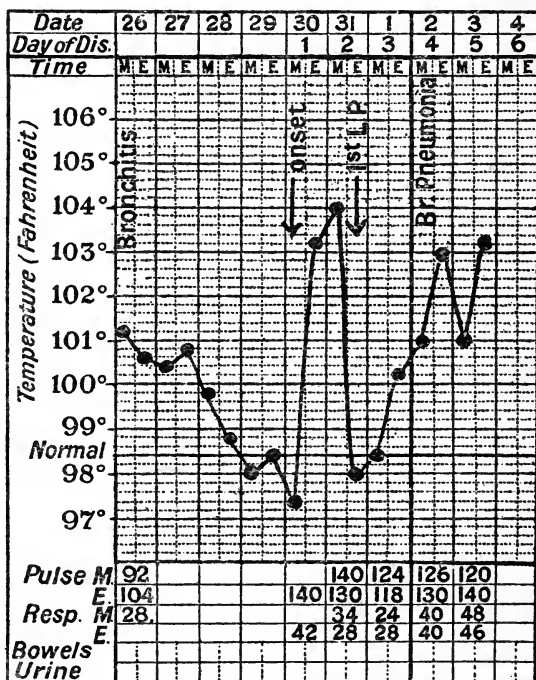
FIG. 4.—Chart of an acute case dying on the fifth day of illness (Case V.)—illustrating the onset of the disease with an initial fall in temperature to subnormal, followed by a rapid rise.

scattered rhonchi were heard chiefly over the left lung, and particularly in the lower lobe posteriorly. The bronchitis progressed satisfactorily, the temperature and pulse rate reaching normal on January 29th.

On the following morning (January 30th) the patient felt quite well and was allowed to sit up. About 11 A.M., however, he had several shivering attacks, and his temperature was found to be 97·4° F. He refused dinner and during the afternoon complained of severe headache; at 6·30 P.M. vomiting occurred, the temperature having risen to 103·2° F. No signs of meningitis were present, the neck being quite supple and Kernig's sign absent. During the night, however, the patient became

delirious, and on the following morning presented the typical appearance of an acute case of cerebro-spinal fever with a profuse purpuric eruption ; lumbar puncture revealed a turbid fluid containing meningococci. He died on the fifth day of illness, broncho-pneumonia having supervened on the previous day (*vide* p. 159).

In the second case, aged 19 years, the primary onset, though sudden and abrupt, led up to only an abortive attack of the disease, lasting less than 36 hours. The patient then felt perfectly well for three days, the temperature remaining normal. On the fourth day following the abortive attack, he felt " chilly " during the morning and shivered several times ; the temperature was then 97·2° F. The patient had no inclination to eat, and in the evening, complained of intense headache. Vomiting occurred during the night, and on the following morning he was delirious and exhibited a temperature of 103° F. (Fig. 23, p. 163). This case (Case XXI.) is more fully described on p. 162.

The rise in temperature, often to 103° or 104° F., which follows the onset of the disease, is sometimes absent in fulminating cases ; some, indeed, die without ever exhibiting pyrexia. In mild cases the initial rise in temperature is often comparatively slight.

A considerable fall, usually to normal or to about 99° F., almost invariably follows the initial evacuation of turbid or purulent cerebro-spinal fluid (*vide* Treatment, p. 415) ; after a varying interval, however, this is followed by a rise in temperature in all but abortive cases (Figs. 4, 6, 9, 17 and 49).

The pyrexial course is much modified by lumbar puncture and serum treatment, and is usually irregular throughout ; it does not, therefore, conform to any definite or characteristic type. Horder, however, figures the chart of a patient, aged 39, suffering from cerebro-spinal fever, not treated by lumbar puncture or serum injection but only by urotropine administered by the mouth ; this chart probably represents a course of pyrexia natural to the disease. For the first two weeks, the case showed a more or less continued fever between 100° and 103° F. with occasional slight remissions, followed by a temperature of intermittent type (97°-102° F.) during the third week, after which the patient recovered. The majority of our cases, treated by the intrathecal administration of serum, continued lumbar puncture, and vaccine, exhibited a very irregular remittent pyrexia (*vide* Figs. 5 and 6) ; in a minority it was inclined to be intermittent (Fig. 7), but in all cases was invariably somewhat irregular. Several cases, at first exhibiting

FIG. 5.—Chart of an acute case of Cerebro-spinal Fever becoming subacute and recovering after the fourth week of illness—illustrating the irregular course of pyrexia. Treatment consisted in continued lumbar puncture and serum administered intrathecally.

a generally remittent pyrexia, showed an intermittent temperature
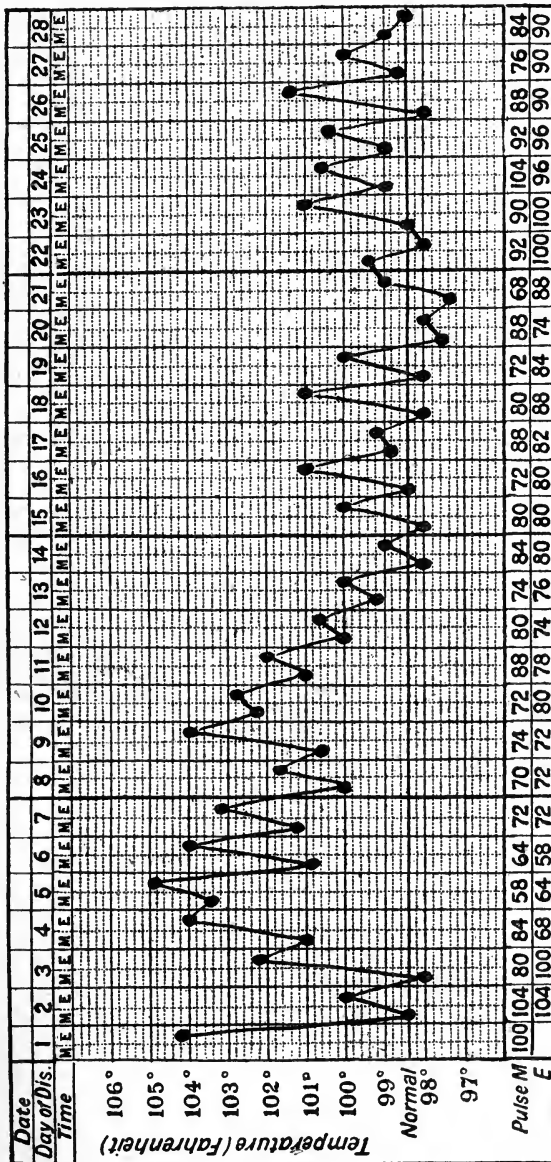
FIG. 6.—Chart of an acute case of Cerebro-spinal Fever admitted to hospital on the first day of illness and becoming subacute. The patient had recovered by the 30th day—illustrating the irregular course of pyrexia.

later in the course. As a rule the evening temperature is higher than that recorded in the morning.

6

The pyrexial course in those cases termed recrudescent (*vide* p. 161) is characterised by its irregularity, one or more apyrexial periods each being followed by further rises in temperature ; the fever then continues for a variable number of days before again falling to normal.   Several such recrudescences of fever may occur during the course, each usually coinciding with an increase in the meningeal symptoms (Figs. 23 and 24).

In many cases, other than recrudescent, running a somewhat protracted course, the temperature may be raised considerably at the onset and for the first week of illness, but will often fail to show any further rise above 100° F. during the remainder of the course.
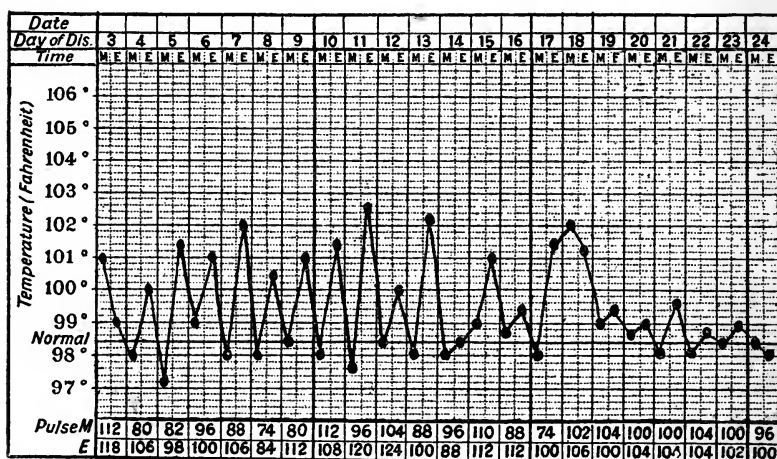
FIG. 7.—Chart of an acute case admitted to hospital on the third day of illness and recovering after a course of 24 days—illustrating an intermittent type of pyrexia.

In the posterior basic type of infants, pyrexia is frequently absent by the end of the first week.

The termination of pyrexia, in the majority of cases recovering, occurs by lysis (Fig. 5). Cases are not uncommonly met with, however, which exhibit a distinct crisis, in some instances both as regards the pyrexia and the symptoms. A crisis is most frequently seen in abortive cases (*vide* p. 152), but apart from these it may be shown by other acute cases ; an example, in a patient aged 32 years, occurring after a pyrexial course of 14 days, is illustrated by Fig. 8. The patient was acutely ill and yielded a definitely purulent fluid when lumbar puncture was first performed on the fourth day of illness (Case VIII. p. 91). The purulency of the cerebro-

spinal fluid, however, gradually decreased until it became merely slightly turbid, and on the day following the crisis (15th) the cerebro-spinal fluid, for the first time, was quite clear. On microscopical examination, this fluid showed no more than the normal number of cells and organisms were absent. In a few cases, the day of crisis coincides with the withdrawal of the first sample of clear cerebro-spinal fluid obtained; this was seen in the case of a child, aged eight years, whose illness terminated by crisis during the third week.

Towards death in acute cases, a rapid rise of temperature, often

Date Day of Dis. Time	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Pulse M					70	80	90	106	104	110	110	124	110	120	96	96	84	80	80	80	80	
Pulse E				60	60	86	110	104	124	120	104	106	110	120	100	84	80	84	76	84	76	
Resp M					20	20	30	30	32	32	30	30	30	38	26	22	20	20	22	20	20	
Resp E				20	20	26	28	30	30	30	34	30	30	30	24	20	24	24	24	20	20	
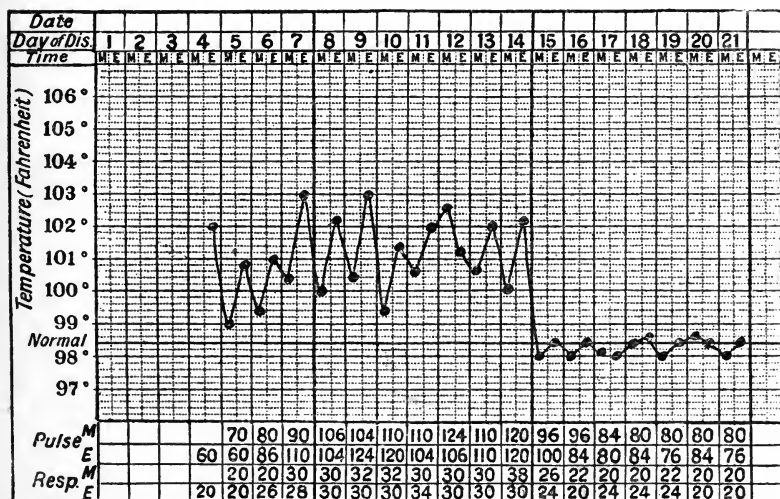
FIG. 8.—Chart of an acute case admitted to hospital on the fourth day of illness and terminating by crisis on the 14th day. On the 15th day the cerebro-spinal fluid was quite clear for the first time since admission. (Case VIII. p. 91.)

to a considerable height (106°-107° F.), is frequently met with. Of 12 cases dying comatose between the third and twelfth days of illness, in no less than 10 did the temperature reach 103° F. or over just prior to death; in two, a temperature of 107° F. was recorded (*vide* Fig. 9). This fatal rising was attributed by H. W. Berg to a paralysis of the heat-regulating centre in the brain. In fulminating cases and a few acute ones, the collapse before death may lead to a subnormal temperature.

Hyperpyrexia during the Course.—Isolated rises of temperature to 104° or 105° F. are met with comparatively often, but a more or less continuous hyperpyrexia, as for instance a rise of evening

temperature to 104° F. or over on successive days, is somewhat infrequent; we have observed this condition in a few cases only, all of which proved fatal.

In the following case two distinct hyperpyrexial periods occurred; during the course of 31 days, meningococci were invariably present in the cerebro-spinal fluid.
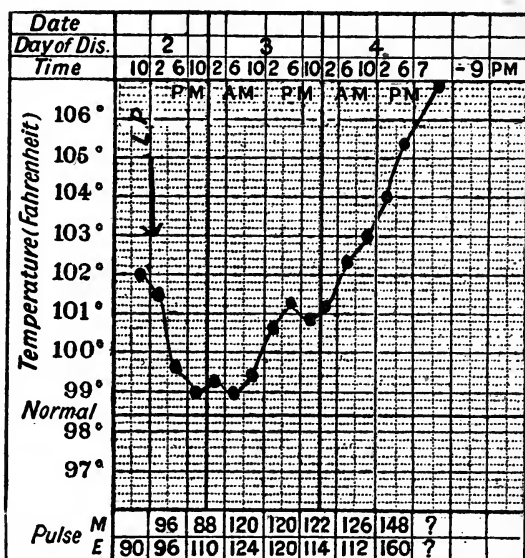
Fig. 9.—Chart of an acute case admitted to hospital comatose on the second day of illness and dying on the fourth day—illustrating the rise of temperature to a high degree towards death,

CASE VI. (Fig. 10).—The patient, aged 25, was admitted on the second day of illness in a state of unconsciousness with occasional delirium and a well-marked petechial rash distributed practically all over the body, including even the face; occasional purpuric spots were also present. The onset had occurred suddenly with headache and vomiting on the previous day. On lumbar puncture, a turbid fluid was obtained which was found to contain numerous meningococci chiefly extracellular. Although cases exhibiting such a rash often die within a few days, the course in this case continued for 31 days before a fatal termination occurred.

The first hyperpyrexial period lasted from the 5th until the 11th day inclusive, and the second period somewhat irregularly between the 15th and 24th days. The rise in temperature to 104·2° F. on the evening of the 5th day was accompanied by increased head retraction but diminution in the rigidity of the legs. The pulse rate was also increased from 112 to 132 per minute. With the gradual fall to 100°

towards the morning of the 7th day, fluid was detected in the right
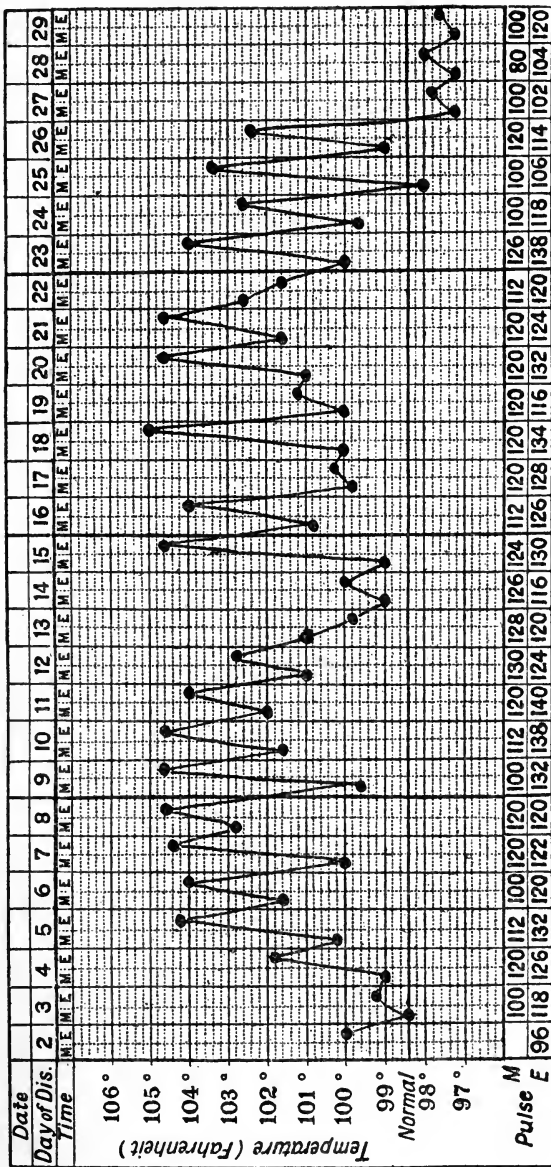
Fig. 10.—Chart of an acute case of dying on the 31st day of illness—illustrating hyperpyrexia. Two hyperpyrexia periods are seen, the first occurring from the 5th to 11th day inclusive, and the second somewhat irregularly between the 15th and 21st days. (Case VI.)

knee-joint, which on aspiration proved to be purulent (vide Chapter VIII. p. 195); there was, however, no improvement in his general condition. The subsequent rise in temperature was accompanied by increased

delirium. At this time, the cerebro-spinal fluid was turbid and contained numerous meningococci but relatively few cells. Throughout the first hyperpyrexial period the patient was restless, delirious and incontinent; the pulse rate usually varied directly with the temperature. The cessation of hyperpyrexia on the 12th day coincided with the disappearance of fluid from the knee-joints and of albumin from the urine; there was also a slight improvement in the patient's mental condition. Forty to fifty c.c. of cerebro-spinal fluid were obtained daily throughout this period, and invariably it contained meningococci. A blood culture taken on the 12th day proved sterile.

The second hyperpyrexial period occurred irregularly between the 15th and 21st days of illness. The only noticeable change during this period was that retention of urine replaced the previous incontinence.
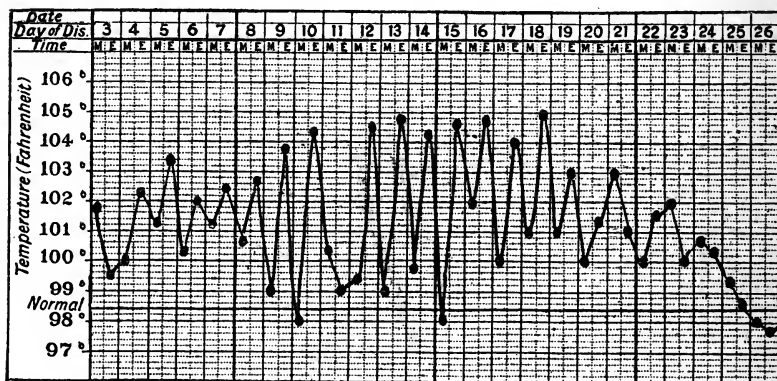
Fig. 11.—Chart of an acute case—illustrating hyperpyrexia occurring from the 12th to 18th day. The case terminated fatally on the 26th day of illness. (Case VII.)

Meningococci, in varying numbers, were found in the cerebro-spinal fluid until the day of death.

As regards treatment, the patient was given 30 c.c. of anti-meningococcal serum intrathecally on each of the first ten days of observation. For four days it was then withheld, lumbar puncture alone being performed; following this, serum was resumed for a further ten days, although without definite effect either on the meningococci in the cerebro-spinal fluid or upon the clinical condition of the patient. No symptoms referable to the serum were ever observed. Finally, death occurred on the 31st day of illness, paraplegia being present during the last five days.

CASE VII. (Fig. 11).—A boy, aged four years, was admitted to hospital acutely ill, with well-marked neck rigidity, positive Kernig's sign and incontinence of urine; a petechial rash was present over the trunk. On lumbar puncture a turbid fluid was obtained, containing meningococci both intracellular and extracellular. The patient con-

tinued severely ill, at times comatose and invariably incoherent ; head retraction developed and general muscular rigidity became pronounced. Diplococci were found in the cerebro-spinal fluid whenever sought for, and he exhibited little or no response to serum administration (the case, however, occurred early in 1915, when the brand of serum used was unsatisfactory, *vide* p. 395). Soamin, administered intramuscularly in 2-gr. doses, was also without effect.

A hyperpyrexial period occurred from the 12th to the 18th day inclusive, the evening temperature rising to 104° or over ; no definite complication developed during this period beyond paralysis of the right external rectus muscle. The case terminated fatally, after a severe course, on the 26th day of illness.

It will be noticed that in both the above cases meningococci persisted in the cerebro-spinal fluid throughout the course of the disease.

Pyrexia persisting after the Termination of Meningitis.—When meningitis has definitely terminated, as indicated by the withdrawal of a perfectly clear and microscopically normal cerebro-spinal fluid on lumbar puncture, and there exists no evidence of hydrocephalus, some degree of pyrexia may occasionally persist. In some cases, this is due to the presence of a complication which has appeared late in the disease, such as an arthropathy, pyelitis, etc. In many instances, however, no adequate cause can be demonstrated. One of our cases, acutely ill and running a course of four and a half weeks, showed at the end of this period a perfectly normal cerebro-spinal fluid and a complete absence of all subjective symptoms ; a remittent pyrexia (101°-99° F.), however, continued for eleven days after the first sample of clear and sterile cerebro-spinal fluid was obtained. To account for this temperature, no satisfactory cause could be found ; there were no physical signs of meningitis or other condition beyond the extreme weakness to be expected after recovery from a severe illness. Lumbar puncture, performed on two occasions, four and eight days after the termination of meningitis, continued to reveal a clear and sterile cerebro-spinal fluid under no increased tension. Finally, the temperature fell by lysis and did not recur. Another case, aged 19 years, continued to show an intermittent pyrexia (97·8°-100° F.) for eight days following the withdrawal of normal cerebro-spinal fluid. The temperature reached normal, however, almost immediately after the administration of a dose of polyvalent vaccine (1000 millions) and did not rise again.

Pyrexia due to Serum Disease.—A serum-treated case, recovering

before the ninth or tenth day following the onset of the disease and the temperature then being normal, may show a secondary rise of temperature to 100° F. or thereabouts, following closely upon the primary decline. This will be found to occur within 8-14 days after the first administration of anti-meningococcal serum ; the short temperature curve is characteristic and often exists with or follows immediately upon a serum rash. It is one of the manifestations of " serum disease " and must not be mistaken for a recrudescence of meningitis (*vide* Treatment, Chapter XVIII. p. 463).

Pyrexia during Convalescence.—During convalescence, the temperature in some cases is inclined to be unstable, temporary and apparently causeless rises being observed. Such instability may continue for as long as three or four weeks after the disappearance of meningitic symptoms. This pyrexia is unassociated with any physical signs ; the hamstring muscles show no increased rigidity, and the neck remains as supple as prior to the rise. If lumbar puncture be performed, the cerebro-spinal fluid will be found normal in all respects. These rises of temperature are, further, unassociated with any increase in the pulse rate, which remains at its previous level. Also, they appear to affect the patient very little ; at the most he may complain of a slight headache. We have observed this " irritability " of temperature not only in convalescent patients who are up and about, but also in cases prior to their being allowed out of bed ; the rises of temperature are not, therefore, the result of exertion on a debilitated system. They were observed in about 5 per cent of cases recovering, all of whom suffered from a severe form of the disease. The pyrexia is illustrated by Fig. 12, p. 89. A slight disturbance of the heat-regulating centre is a possible explanation.

Symptoms associated with the Cardio-vascular System.—*Pulse.*— In the early stages of the disease, following the initial onset and prior to the involvement of the meninges, the pulse rate is inclined to be somewhat rapid. Thus, in two cases seen on the first day of illness and in whom lumbar puncture revealed a normal cerebro-spinal fluid, the pulse rates were 104 and 120 per minute respectively ; the temperature in the former case was 104° and in the latter 103·8° F. Within 18 hours, both patients yielded a turbid cerebro-spinal fluid containing meningococci. Meningococci were cultivated from a sample of the blood taken from the second patient at the time of the first lumbar puncture—when clear fluid was withdrawn (Case II. p. 63).

With the development of meningitis, however, the pulse rate
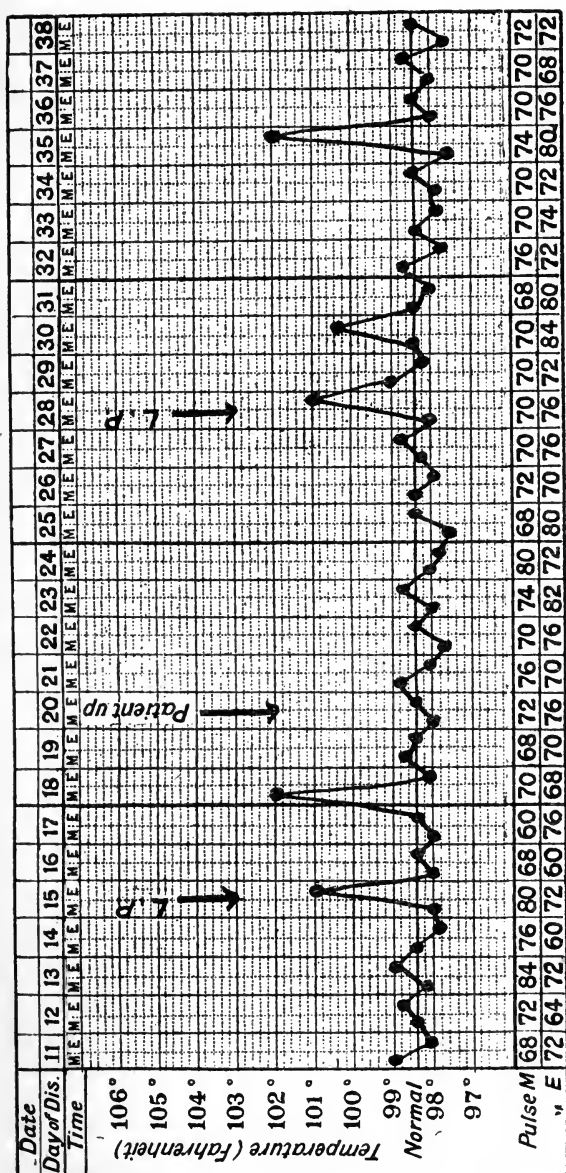
Fig. 12.—Chart illustrating the instability of temperature occasionally observed during convalescence from cerebro-spinal fever, in association with which no definite physical signs can be demonstrated. It will be noticed that there is no corresponding rise in the pulse rate. The patient, aged 39, had had a somewhat severe course of illness of 22 days' duration. The chart records the temperature from the 11th day following the withdrawal for the first time of clear cerebro-spinal fluid. The patient was allowed up on the 22nd day of convalescence; lumbar puncture performed at the time of the temperature rises (15th and 28th days of convalescence) yielded a normal cerebro-spinal fluid under no increased pressure.

speedily falls, and, in the majority of cases, is comparatively slow in proportion to the temperature by the time the patient comes under

observation. In the two cases mentioned above, the pulse rates were 80 and 96 respectively just before the withdrawal of the first *turbid* cerebro-spinal fluid. Of 58 cases, on admission to hospital, the pulse was 96 or under in 45, and in 31 it was not above 84 ; turbid or purulent cerebro-spinal fluid was obtained on lumbar puncture in all cases.

The pulse rate may frequently be slow in association with considerable pyrexia ; for instance, in one case admitted profoundly delirious on the second day of illness, it was 64 per minute, the temperature being 103·4° F. In a second patient the pulse was 80, in spite of the presence of a temperature of 104·2° F. The fact that a comparatively slow pulse exists in association with pyrexia, constitutes in many cases an important diagnostic feature. In fulminating cases, or in those dying within a few days of the onset, no slowing of the pulse rate may be observed ; it varies in rapidity, but is seldom below 110 per minute, and gradually increases towards the end of the course (Fig. 16, p. 143).

Subacute cases, when not recognised as suffering from cerebrospinal fever until comparatively late in the disease, may show a pulse rate of 100 per minute or over when eventually they come under treatment. For instance, in three subacute cases not arriving under our care until after the twelfth day of illness, the pulse rates on admission were as follows : 98, 110 and 120.

During the course, the pulse frequency varies from day to day ; in the majority of cases it averages about 80 per minute, but may be as low as 60 or even 50. Very slow pulse rates are probably due to inhibition produced by action on the centres of the vagus nerve. As a rule, the pulse rate shows little or no relation to the fluctuations of temperature. In the presence of hyperpyrexia, however, it may increase *pari passu* with the rising temperature (*vide* Fig. 10). It is not uncommon for a case to show no rise of pulse rate above 80 throughout the course of meningitis ; in those cases, however, becoming subacute and continuing for a somewhat protracted course, the pulse in general tends to become more frequent during the later stages. Thus, in one case of a recrudescent type and running a course of 12 weeks before recovering, the pulse rate was seldom above 100 per minute during the first eight weeks ; afterwards, however, it averaged 120 and occasionally reached 140. A subacute case running a course of 28 days showed, during the last seven days, a rise of pulse rate from 70-90 to 110-120 ; the increased rate persisted for a week after recovery. In marked contrast, another case,

recovering after a severe course of 40 days, seldom exhibited a pulse rate of above 80 throughout the illness. A dicrotic pulse may sometimes be met with ; in cases of our series it was usually observed about the 4th-7th days of the disease.

In cases developing internal hydrocephalus, the character of the pulse rate gradually changes, becoming very rapid and feeble.

Heart.—Clinically, the heart is frequently unaffected to any appreciable extent. Post mortem, however, varying degrees of cloudy swelling of the heart muscle, together with a certain amount of general dilatation, are almost invariably found in acute cases dying within the first eight or nine days. Of ten such cases which came to autopsy, cloudy swelling was present in all ; also the heart cavities were dilated, the right side being chiefly affected. In fulminating and some acute cases, impairment of resonance may sometimes be found to the right of the sternum. Also, that in acute cases left-sided dilatation can occasionally be demonstrated clinically is shown by the observations on the following case :

CASE VIII. (Fig. 8).—The patient, aged 32 years, was admitted to hospital in a profoundly delirious condition on the 4th day of illness. The onset had occurred suddenly with headache and vomiting, and delirium had been present for two days. On admission, the temperature was 102° F. and the pulse 60 ; retention of urine was also present and the usual signs of meningitis were well marked. Lumbar puncture revealed a purulent fluid containing numerous meningococci both intracellular and extracellular.

Delirium and retention of urine, with occasional stupor, persisted until the 12th day of illness ; following this the patient rapidly improved, and on the 15th day the cerebro-spinal fluid was quite clear. The pyrexia was irregularly remittent throughout, varying between 99° and 103°, and terminating by crisis on the 14th day of illness (Fig. 8). Specific treatment consisted of anti-meningococcal serum administered intrathecally in 30-c.c. doses each morning until the 10th day ; the doses were also repeated on the evenings of the 6th and 7th days. Following the 10th day, lumbar puncture was repeated daily until a clear cerebro-spinal fluid was obtained. Three doses of autogenous vaccine were also given at intervals (*vide* Treatment, Chapter XVIII. p. 429).

Throughout the illness the patient's circulation was very poor, and particularly during the 6th, 7th and 8th days ; this was treated by giving hot saline solution per rectum and digitalin hypodermically in 1/100-gr. doses. The following table shows the condition of the heart on respective days of the course :

4th day (admission)	Cardiac impulse 1 in. within nipple line ; pulse :						60-80.
5th-7th days	,,	,,	1 ,,	,,	,,	,,	80-110.
8th-9th ,,	,,	,,	just	,,	,,	,,	104-124.
10th day	,,	,,	,, outside	,,	,,	110-130.
11th ,,	,,	,,	,, on	,,	,,	100-120.
12th ,,	,,	,,	,, within	,,	,,	90-124.
13th-16th days	,,	,,	½ in. ,,	,,	,,	84-120.
20th day	,,	,,	1 ,,	,,	,,	,,	80-84.

At no time was a murmur present.

Expiratory inhibition of the auricle is occasionally met with, but the heart is rarely slowed below a rate of 50 per minute. Death from cardiac failure is comparatively infrequent in uncomplicated cases.

Other conditions affecting the heart are dealt with among the complications of the disease (Chapter VIII.).

Epistaxis.—Epistaxis sometimes occurs. In one of our cases, it was present on the 5th, 6th and 7th days of an acute attack of the disease, while in a second it occurred at the onset, following the initial vomiting.

Ciliary Hyperaemia is often present in cases when they first come under observation ; it may lead to conjunctivitis.

Symptoms associated with the Respiratory System.—*Respiratory Rate.*—In the majority of cases, during the course of the disease the respirations are only slightly quickened (30-34 per minute). When patients first come under observation, however, there is usually little or no increase ; it is frequent to find only 24 respirations per minute accompanying a temperature of 104° F. ; in general, the respiratory rate bears very little relation to the degree of pyrexia. In fulminating cases, respiration may be rapid (40-50 per minute) and associated with considerable dyspnoea ; also, in acute cases dying within five or six days, they are frequently as high as 60 per minute during the last day or two. The number of respirations per minute often varies from time to time, and under general anaesthesia, an increased rate may fall to normal, thus suggesting an acceleration of central origin. Respiration is seldom affected by lumbar puncture and the withdrawal of cerebro-spinal fluid. The introduction of serum into the subarachnoid space, however, may affect the respiration ; this latter subject is fully discussed in the section on Treatment (Chapter XVIII. p. 419).

The pulse-respiration ratio is variable and rarely exhibits a regular increased ratio as seen, for instance, in pneumonia. When the latter disease occurs as a complication of cerebro-spinal fever,

however, the respiratory rate at once rises (from 26 to 40 in one case, and from 28 to 46 in another) and bears a more constant relation to the variations of the pulse rate.

Irregularities of Respiration. — Connor and Stillman in 1912, while studying respiration in meningitis, found irregularities in 95 per cent of cases. The irregularities may be classified as follows :

(*a*) Cheyne-Stokes Respiration.—This type is well known and may occur towards death in a variety of conditions. It is characterised by periods of apnoea, and following each of these periods, the respiration begins gradually and increases in depth until a laboured climax is reached. The respirations then gradually subside in the reverse manner to that in which they arose, finally terminating in apnoea. Cheyne-Stokes respiration is present only as a terminal phenomenon both in acute and chronic cases.

(*b*) Biot's Respiration.—In 1878, Biot described a type of respiration consisting in a constant irregularity of both rhythm and depth of the individual respirations, associated with periods of apnoea of varying length and occurring at irregular intervals ; not uncommonly some respirations are of a deep sighing character. Biot's respiration is generally observed late in the disease and is of bad prognostic import.

(*c*) An Undulatory Type.—There are variations both in the frequency of respiration and in the depth of inspiration, but no periods of apnoea occur. This type is not infrequently seen in association with hydrocephalus.

In two acute cases, during the first two weeks of illness, we frequently observed what might almost be termed an " asthmatic " type of respiration. This consisted of a short inspiration, usually through the nose, followed by a long blowing expiration through the mouth, accompanied by pursing of the lips ; it was present as a rule for three or four hours at a time. Both cases were more or less delirious throughout the period mentioned, although occasionally, if roused, they would answer questions ; both patients recovered after courses of 23 and 28 days respectively. Throughout, the lungs were normal in each case.

Fairley and Stewart, in three or four acute cases all terminating fatally, observed the presence of regular and deep sighing respirations ; those cases which came to autopsy all showed the presence of well-marked internal hydrocephalus.

Hiccough may occur in association with a distended bladder ; catheterisation will give relief.

Respiratory Failure.—Death frequently occurs from sudden respiratory failure, the heart continuing to beat for an appreciable period after respiration has ceased. It probably results from some interference with the circulation to the fourth ventricle.

Rashes.—Contrary to general supposition, the rash in cerebro-spinal fever is an extremely variable feature. In many cases no rash ever appears; it may be absent even in fulminating cases. As regards frequency of occurrence, a rash of varying type was observed in 53 per cent of our cases. The characteristic rashes are three in number: (1) Maculo-papular, (2) Petechial and (3) Purpuric, the latter being a more intense form of the petechial.

(1) *Maculo-papular Rash.*—When present, this rash usually appears within the first four or five days of illness; occasionally, however, it may occur as late as the seventh or eighth day. It frequently appears in the form of discrete rose spots, but the colour may vary from scarlet to purple. In one of our cases the macules were pale lilac in colour. At times, the eruption is entirely macular, but often the cutis is distinctly raised, constituting a definite papule; as a rule the spots do not fade on pressure. In size, the lesions differ considerably, varying from 1 millimetre to 5 or 6 millimetres in diameter; this variation in size, as Foster and Gaskell point out, is not due to the outbreak of successive crops of the lesions, but persists from the time of their first appearance. The distribution is fairly uniform, the rash first appearing on the trunk, usually the abdomen, and subsequently on the hips and extensor surfaces of the thighs and forearms; finally, it may develop on the backs of the hands and dorsal aspects of the feet. Occasionally a macular eruption may assume a form resembling a measles rash with an irregular distribution.

The eruption fades rapidly, and at the end of four days nothing but a bluish staining remains. Some authors regard the maculo-papular rash as the true specific eruption of the disease.

This rash was not observed in more than 20 per cent of our cases; it usually appeared on the second, third or fourth day of illness, and in some instances petechiae were also present. Of 15 cases of one series showing a maculo-papular eruption, nine recovered and six died.

(2) *Petechial Rash.*—This consists of small purplish papules which do not fade on pressure. The petechiae are especially numerous at points where pressure is liable to occur; thus, they are frequent on and about the knees, elbows and shoulders. The rash

is sometimes present on the first day of illness and seldom appears later than the third day.

This type of rash, apart from those cases in which it co-existed with a purpuric eruption, was seen in 31 per cent of our cases. In some instances the petechiae were entirely confined to the lower extremities ; others, however, showed them on the arms in addition, together with a few scattered over the trunk. In 30 per cent of these cases a maculo-papular rash was also observed.

(3) *Purpuric Rash.*—The purpuric rash is a more intense form of the petechial, and in most cases which exhibit it many petechiae are also present. The eruption consists of large dark purple spots, varying in size from that of a pea to that of a large plum ; in distribution the lesions are somewhat variable, and may be found anywhere about the body. We have seen vibices, as the purpuric spots and patches are sometimes termed, most frequently on the back, buttocks and hips. In many cases, they were also present on the extensor surfaces of the arms and legs, while three patients exhibited them even on the face. This type of rash is met with only in fulminating or in very acute cases, and almost invariably foreshadows a fatal result.

Five fulminating cases with a purpuric eruption died within 48 hours of the onset of the disease ; in each case large plum-coloured vibices were present on the trunk and petechial spots were scattered almost all over the body, the latter being especially numerous on the extensor aspects of the arms and legs. Three acute fatal cases with a similar rash died within four days of the onset of the disease. Another acute case was admitted to hospital on the second day of illness, with a petechial rash particularly well marked on the arms and legs, but also invading the face and neck ; in addition, several purpuric spots were present, a large one being noticed to involve almost the whole of the right eyelid. The rash began to fade on the fourth day. Eventually the patient died after a severe course of 31 days' duration. In another patient, who recovered after 40 days of illness, a few purpuric spots were seen on the legs only. In Case II., fully described on p. 63, an intense purpuric eruption appeared prior to the involvement of the meninges, that is, during the pre-meningitic stage, and while the cerebro-spinal fluid was still clear and free from organisms. The patient recovered, and owing to the comparative rarity of such a result in a case of cerebro-spinal fever exhibiting numerous and well-marked vibices, the subsequent history of the rash is of interest. The larger patches, contrary to

expectation, did not fade, but by the seventh day of illness had become vesicular; on the ninth day a few were pustular; these, on breaking down, left a distinct excavation, which did not heal completely for three or four weeks. Somewhat similar cases, in which ulceration occurred in the larger purpuric patches, have been recorded by Bovaird, Robb, Elliott and Kaye, and H. D. Rolleston.

Meningococci may frequently be obtained on blood culture from cases exhibiting a purpuric rash, and diplococci may occasionally be seen in blood films taken from the vibices themselves. Netter reports a case in which meningococci were cultivated from the vesicle forming on the site of a purpuric patch.

In our cases showing a petechial rash with or without a purpuric eruption, the mortality was 44 per cent, as compared with 18 per cent in cases exhibiting no rash.

(4) *Other Rashes.*—Mottled erythematous rashes of a transient nature may occur at almost any stage of the disease. In some cases an erythema may be observed during the pre-meningitic stage; C. P. Symonds, for instance, mentions three cases in which an erythematous rash appeared before any symptoms of meningitis. In each case it was transient, lasting only 4-6 hours; in one patient, who was under observation for another condition when he developed cerebro-spinal fever, the rash appeared six hours after the onset of the latter disease. In one of our cases, previously showing a few petechiae on the knees and elbows, an intense scarlatiniform erythema appeared on the fourth day of disease, being distributed over the chest and sides of the abdomen. Osler has described a peculiar diffuse and livid erythema about the extensor surfaces of the extremities, which was accompanied by vesicles filled with blood; after the erythema faded and the vesicles dried, small nodules persisted for a week to ten days. As a manifestation of the general vaso-motor disturbance, localised erythema is frequent, especially about the hips and the knees.

Fairley and Stewart describe a lesion, consisting in the appearance on the buttock of a large, raised and red patch, 2-3 inches square, and having the appearance of a large wheal. In the three cases in which this lesion was noticed, a fatal termination occurred within 24 hours of its appearance. Such a condition was also present in four cases of our series; at first the lesion might easily be mistaken for a burn caused by a hot-water bottle or a sore produced by pressure. In each case, however, these causes could be excluded; one patient, indeed, presented the " wheal " just above the posterior part of the

PLATE II.

HERPES.

An acute case on the fifth day of illness showing a well-marked herpetic eruption.

iliac crest. As with Fairley and Stewart's cases, not one of our four patients lived for more than 24 hours following the discovery of the lesion.

Herpes.—Herpes appears in a considerable number of adult and adolescent cases, but is very rarely seen in patients under two years of age. Of cases in our series, it was present in 35 per cent; in Rolleston's series of Royal Navy cases, herpes occurred in 22·2 per cent.

The date of the appearance of herpes varies from the third to the seventh day, but most frequently it begins to develop on the fourth day. In one of our subacute cases, however, herpes was found for the first time on the tenth day of illness; nevertheless, this is unusual. The following table shows the day of its appearance in 26 cases:

Day of disease on which herpes appeared.				Number of cases.
3rd	.	.	.	2
4th	.	.	.	14
5th	.	.	.	5
6th	.	.	.	2
7th	.	.	.	2
10th	.	.	.	1

In many cases the margins of the lips only are affected, but in others the eruption spreads to the face, involving the chin, cheeks and nose, and not infrequently extending into the ear. In a few cases it also appears on the mucous membrane of the mouth, and Sophian mentions a patient who displayed a large crop on the anterior pillar of the fauces; more rarely the cornea, fingers and toes may be involved.

Of a series of 26 herpetic patients, the eruption was entirely labial in 14; in the remaining 12 the face also was involved to a varying degree. In cases exhibiting facial herpes the circumoral area is a common site of distribution. One case on the fourth day of illness showed extensive herpes around the mouth; by the following day, it had spread to the chin, the nose and both cheeks (Fig. 13). In spite of a tendency to ulcerate, the eruption had quite healed by the 19th day. A second case had labial herpes, and, in addition, a large patch spreading from the corner of the mouth up the right side of the face, involving the right ear, including the external auditory meatus, and spreading on to the neck (Fig. 14). On the fifth day, in another case, the herpes showed a distribution resembling that of lupus erythematosus, the circumoral area entirely

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escaping, and the eruption spreading, butterfly-fashion, from ear to ear on both cheeks and across the nose (Plate II.).

In somewhat rare instances, herpes may occur in situations other than those mentioned above. Netter figures an eruption occurring in the area of distribution of the fifth lumbar nerve, and a second on the sole of the foot, while Sophian mentions a case in which herpes appeared on the knees. In one of our cases, aged 15 years, typical herpes zoster appeared, on the tenth day of illness, along the course of the eighth thoracic nerve ; in another case, a herpetiform eruption was seen on the inner side of the leg, towards

FIG. 13.—The distribution of Herpes in an acute case on the fifth day of illness. The eruption had healed by the 19th day.
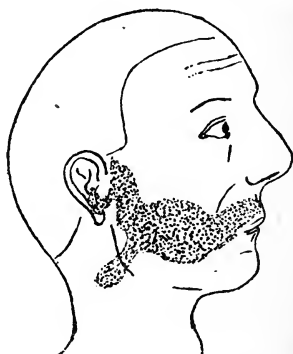
FIG. 14. — The distribution of Herpes in an acute case on the fourth day of illness.

the lower limit of the cutaneous area supplied by the internal saphenous nerve.

The first sign of herpes is the presence of a hyperaemic patch on which small groups of vesicles appear ; these rapidly increase in size, and their contents subsequently become purulent. Finally, after 5-10 days, the pustules dry up and form scabs. When the eruption is somewhat extensive, it may exhibit a tendency to become haemorrhagic. Meningococci have been found in the pus, taken from herpetic lesions, by Von Drigalski and by Herford.

The presence of herpes has been considered by some authors as a favourable sign, the majority of cases presenting the symptom terminating in recovery. To base a good prognosis on its appearance, however, will often end in disappointment, as cases exhibiting herpes often die. Thus of the 26 cases with herpes mentioned above,

six died (23 per cent) ; of these six, in one case only was the herpes more than merely labial in distribution.

The Urine.—Polyuria is not an uncommon symptom early in the disease ; it may be associated with excessive thirst at any stage during the course. The fluid intake being constant, there is apparently no relationship between the degree of blood pressure and the amount of urine excreted; in some cases, polyuria may be associated with a low blood pressure, while in other cases with a high pressure, the quantity of urine passed is scanty. Netter attributes the occasional polyuria to irritation of the floor of the fourth ventricle.

As regards the ordinary constituents of the urine, Solbeit and Schubert have found that during the acute stage, the urea and phosphates are in excess of the normal, while the chlorides are greatly diminished. Loeper and Gourand describe a urinary syndrome, characterised by polyuria and increased excretion of nitrogen, phosphates and chlorides.

Albuminuria.—In acute cases, albuminuria frequently occurs. Of our series, it was present in 43 per cent, although in the majority it occurred only during the first four or five days of illness, and in quantity seldom amounted to more than 0·05 per cent (Esbach). Such albuminuria is unassociated with the presence of casts ; in some cases, however, apart from those catheterised for retention, pus cells were not infrequently found on microscopical examination of the urine. In acute cases dying within seven days, albuminuria is frequently present throughout the course.

The specific gravity of the urine during the albuminuric period may vary from 1005 to 1038, but is usually about 1020.

In two subacute cases, albuminuria was present when they were admitted to hospital on the ninth and tenth day of illness respectively ; after a few days, the urine in one case ceased to contain albumin, but in the other albuminuria continued until the 25th day. A third case, admitted on the second day of illness, showed a urine quite free from albumin for the first eleven days. On the 12th day, however, the urine passed at 10 A.M. was pale yellow in colour and the specific gravity only 1002 ; nevertheless, it contained a trace of albumin. At 6 P.M. on the same day, the urine showed a specific gravity of 1014, together with a fair quantity of albumin. At this time the patient was showing some symptoms of hydrocephalus. Five days later, with the patient's improvement, the albuminuria had disappeared, and did not recur, although the case was not

definitely recovered until the 41st day of his illness. In the above cases no urinary deposit was found beyond urates and phosphates.

Glycosuria.—This is a somewhat uncommon symptom. Glucose was detected in the urine of three of our cases, its presence in two being confirmed by the phenyl-hydrazine test.

(*a*) An acute case, aged 21 years, was admitted to hospital unconscious on the second day of illness. Glucose was present in the urine, together with a trace of albumin. On the following day the patient was conscious, and both sugar and albumin were absent. He improved rapidly, and on the tenth day his cerebro-spinal fluid was quite clear.

(*b*) A subacute case, aged 29 years, owing to his true condition being unrecognised, was not received under our charge until the 13th day of illness. On admission, 0·25 gm. of glucose per litre and a trace of albumin were present in the urine. Glycosuria persisted for six days, that is, until the 19th day of illness. It was then absent for three days, but reappeared on the 23rd day, again ceasing on the 26th day. The final disappearance of glucose from the urine coincided with the improvement, under repeated daily lumbar puncture, of hydrocephalic symptoms—extreme drowsiness, headache, tremulousness and vomiting.

(*c*) A patient, aged 26 years, was admitted to hospital delirious on the ninth day of illness. Sugar had been detected in the urine on the fifth day, and the case had been regarded, prior to admission, as a possible instance of diabetes. By the ninth day, however, glycosuria had ceased, and the patient recovered after a course of 19 days.

It is possible that the appearance of glycosuria is associated with a disturbance affecting the floor of the fourth ventricle, such as pressure from within by distension of the ventricular cavity or by actual changes in the wall substance. As no case in which glycosuria occurred proved fatal, investigation of this point was not possible. In a case of pneumococcal meningitis, however, which terminated fatally after a course of eight days, glucose was present in the urine to the extent of 5·8 gms. per litre. On post-mortem examination, the cavity of the fourth ventricle was found distended with purulent fluid. Also, according to Netter and Debré, the floor of the fourth ventricle frequently shows changes in its ependymal lining. The irritation produced by such lesions may account for the occasional glycosuria and polyuria.

Haematuria.—This symptom may occasionally occur in acute cases. When present, it is usually, though by no means invariably, associated with a purpuric eruption. In one of our patients, aged 19 years, slight haematuria was present from the time of admission

on the third day of illness until the sixth day. The urine was slightly acid, contained a trace of albumin, and the specific gravity averaged 1002. The guiacum test showed the presence of blood, and on microscopical examination blood cells were seen, but at no time were there any casts. The case was very acute at first, but recovered after the short course of eleven days.

Haematuria may also occur in association with a complicating nephritis (*vide* Complications, Chapter VIII. p. 192).

The Presence of Organisms. — According to some authors, meningococci may be isolated from the urine during the initial stages of the disease. Sophian states that organisms were found in the urine of a patient, aged 50, while the cerebro-spinal fluid was still clear ; 24 hours later, a turbid fluid was obtained, containing pus cells and meningococci. Quite apart from the presence of pyelitis or cystitis occurring as complications, Sophian and others consider that organisms may readily be demonstrated in the urine of many acute cases. These findings, however, we are quite unable to confirm, as from many catheter specimens of urine, in no case did we satisfy ourselves of the presence of definite meningococci. The frequency of retention and overflow incontinence of urine during the earlier stages of meningitis, gives every facility, as Gaskell and Foster point out, for various urinary infections to occur. We entirely agree with these authors in their observation that, although a large number of organisms can frequently be obtained, meningococci are conspicuously absent. Finally, even if Gram-negative cocci are obtained in culture, the frequent presence of the gonococcus in the urinary tract and the difficulty of distinguishing this organism from the meningococcus must be borne in mind.

In a few cases (2 per cent), an alkaline urine is met with in association with a B. coli bacilluria.

General Aspect.—The stage at which the average patient most frequently comes under observation for the first time is as follows : He lies in bed, usually on his side, with the limbs in an attitude of flexion, but with the head somewhat extended. He looks profoundly ill ; the face is as a rule flushed and the expression dull. Flushing, however, is inclined to vary from time to time, and may alternate with a certain amount of pallor. Mental irritability is pronounced, and any interference on the part of the observer is greatly resented by the patient, especially that of being turned on his back into the supine position. Usually he cannot be roused, and muttering delirium occurs from time to time.

Subacute cases, in whom consciousness may be quite clear, often present a drawn anxious facial expression and lie very still, complaining of pain on the slightest movement. The limbs are somewhat rigid and, compared with that seen in a more acute case, flexion is comparatively slight. This condition may be noticed particularly in adult patients admitted to hospital after some days of illness.

Symptoms due to Involvement of the Nervous System

Mental Condition.—A variable time from the onset and following the initial vomiting, delirium makes its appearance in the majority of cases. This, in turn, is usually succeeded by a state of stupor, the patient, however, showing considerable irritability to sensory stimuli; finally, should the case remain untreated or fail to respond to the treatment adopted, coma eventually supervenes, in which condition the patient remains until death. Other patients may pass straight into a stuporose state, or become comatose without a preceding stage of delirium.

In the majority of mild and abortive cases, the mental condition remains normal throughout; in others there may be only occasional drowsiness during the first three or four days of illness. In our series of cases, the proportion of adolescent and adult patients in which consciousness remained normal throughout the illness was 14 per cent. In infants and young children, no delirium of course occurs, and definite loss of consciousness, in the early stage of the disease, is rare in patients below three years of age; they may, however, exhibit great restlessness and irritability. As the disease becomes more chronic, young children develop extreme drowsiness and apathy, lying quite motionless, and taking little or no notice of anything; often, however, it is possible to rouse them to take nourishment.

Insomnia is frequently a troublesome feature both in children and adults; to some extent it is accounted for by the presence of severe headache. In other patients it is probably the result of meningeal irritation.

Delirium.—The time of appearance of this symptom varies from within a few hours of the onset in fulminating cases to several days in subacute cases. In most cases it is usually present by the second or third day. In one of our subacute cases, however, delirium did not occur until the 10th day; the patient had been

in a small local hospital where the true nature of his disease was not suspected until delirium supervened. Consequently he had remained without lumbar puncture or specific treatment. In some cases delirium may be preceded by considerable drowsiness.

The actual character of the delirium varies greatly, and also differs according to the type of case. Some cases, usually subacute, may exhibit a delirium which is merely nocturnal, consciousness appearing quite normal during the day-time; in others, it consists of a low muttering for only the first few days of illness. At times a patient will be delirious when left undisturbed, yet when roused, answer questions quite intelligently. Occasionally, short periods of delirium may alternate with intervals during which the mind is perfectly clear. In acute cases, however, there is often great restlessness and considerable excitement, difficulty being experienced in keeping the patient in bed. Such cases may be noisy, violent or maniacal, and we have known them diagnosed as suffering from delirium tremens and acute mania.

In most cases terminating favourably, the delirium is confined to the first week, consciousness rapidly becoming normal with improvement in the general condition. Other cases, however, may exhibit delirium for a longer period ; one of our acute cases was delirious until the 11th day of illness ; on the 14th day the cerebro-spinal fluid was perfectly normal, and the patient stated that he felt quite well.

Recrudescent cases often exhibit renewed delirium coinciding with a recrudescence of pyrexia and meningeal symptoms, the mental condition having been normal during the intervening period. In one of our cases, no delirium was present during an initial abortive attack, but occurred with the subsequent recrudescence four days later (Case XXI. p. 162).

The type of case we have described as the progressively purulent (*vide* Course, Chapter VII. p. 156), in which the cerebro-spinal fluid gradually becomes increasingly dense and more purulent, frequently shows distinctive mental changes. The delirium is usually mild at first, but increases towards the 4th-7th day ; definite delusions are then present, and visual hallucinations are sometimes a marked feature. Thus, one case, an alcoholic, continually saw beer bottles and casks of whisky, and a second saw plates of sausages by his bed. Death may occur in these cases during the delirious stage, that is, without the supervention of coma. In fulminating cases the delirium may continue for a few

hours only, being rapidly succeeded by coma; in acute fatal cases dying within 4-7 days of the onset, delirium frequently alternates with a stuporose condition.

Delirium was present at some stage of the disease in 75 per cent of our cases.

Stupor.—In the majority of cases, the initial delirium is succeeded by stupor; in our experience, this is the state in which patients are most frequently received into hospital. As a rule, the patient lies on his side with the limbs in an attitude of flexion; he takes no notice of questions, but if touched is found to be extremely irritable. He is particularly resentful of any attempt to turn him into the supine position, insisting on lying on his side. There is also considerable hyperaesthesia, as shown, for instance, by the active withdrawal of the leg on attempting to elicit the plantar reflex. It is usually impossible to rouse the patient sufficiently to answer questions; occasionally he may mumble incoherently when addressed, or exhibit a brief period of delirium. Often, however, fluids poured slowly into the mouth from a feeding-cup are swallowed fairly well.

A state of irritable stupor was observed in 40 per cent of our cases. In several instances the response to initial lumbar puncture and serum injection was dramatic, the patient's consciousness being normal by the following day.

In acute fatal cases, the stupor is succeeded by coma of increasing depth.

The mortality among our patients exhibiting a stuporose condition was 25 per cent.

Occasionally, at a later stage of the disease, a different type of stupor may be met with. For instance, a patient, aged 24 years, was extremely drowsy, with occasional periods of delirium, during the first four days following his admission to hospital on the third day of illness. On the eighth day he became stuporose, lying apparently conscious, yet staring stupidly if addressed, and taking no notice of requests such as " put out your tongue," etc. On the following day the patient was merely drowsy, and by the 16th day had quite recovered. In cases developing internal hydrocephalus, a state of complete apathy and stupor may alternate with periods of muttering delirium.

Coma.—In acute fatal cases, and usually in those remaining untreated for a number of days, delirium or stupor is sooner or later succeeded by coma. Some cases, as mentioned previously (p. 71),

may pass straight into coma without any preceding delirium ; most frequently this occurs in fulminating cases, but may be met with in other acute cases (*vide* p. 71).   The vast majority of cases terminating fatally die in a comatose condition ; exceptions are occasionally met with especially in the progressively purulent type of case (*vide* Course, Chapter VII. p. 157).   The presence of coma, however, does not necessarily indicate that the case is hopeless ; we have seen patients quite comatose and unresponsive to stimuli, with mucous rattling in the trachea, who finally have recovered.

True coma was observed in 33 per cent of our cases, the mortality of such cases being 80 per cent.

Other Mental Changes.—Some of the more chronic cases, particularly if hydrocephalus be present, may exhibit certain peculiar mental features.   For instance, amnesia for recent events only may be met with, the mind otherwise appearing normal.   This is illustrated in the following cases :

CASE IX.—A subacute case, aged 25 years, died of hydrocephalus on the 54th day of illness.   About the 28th day he appeared to answer questions quite normally, but, on further examination, it was found that he had no memory for recent occurrences, while events in his past life were perfectly clear, *e.g.* he was entirely wrong regarding what he had eaten for breakfast and also as to the visitors he had seen that afternoon.   He was able to state quite correctly, however, the day on which he joined the army, the date of his marriage, and the nature of his employment in civil life.   At this time there were no distinctive signs of hydrocephalus.

CASE X.—A patient, aged 23 years, exhibited a somewhat similar condition to the above during the third week of his illness, when the usual signs of internal hydrocephalus were beginning to develop. The patient was unable to remember having seen his mother, and said that he had not seen her for a week, although, in fact, she had left him only a few minutes before.   On the other hand, he gave his correct age, date of birth, and the name of the firm for which he had previously worked.   Some days later he was talking after the fashion of a baby, yet obeyed commands quite well.   Also, complete loss of orientation was frequently noticed when the consciousness, otherwise, was practically clear.   The patient eventually recovered after a course lasting about 40 days.

Other features of the above two cases are dealt with on pp. 225 and 227 (Internal Hydrocephalus, Chapter IX.).

Occasionally definite delusions may occur ; thus, one patient, during the second week of illness, frequently carried on long conversations with people he knew and imagined to be sitting beside

his bed. At other times his mind was perfectly clear. Reference has already been made to the hallucinations of progressively purulent cases (p. 103).

Rambling incoherence, puerility, emotionalism and various temperamental changes may also be observed during the course of the disease. In a few instances, such changes may persist for a short period after recovery from meningitis. As a rule, however, all mental symptoms disappear during convalescence. Apparent exceptions are mentioned by Sophian, who remarks upon certain states, occurring late in the disease, resembling typhoidal insanity and persisting into convalescence for several weeks, and then suddenly disappearing.

Condition of the Sphincters.—In a considerable number of cases there is loss of control of the sphincters ; they were affected at some time during the course of illness in no less than 60 per cent of cases of our series.

Retention of urine is often an early symptom, and may be found present in some cases shortly after the appearance of delirium. Even should the patient, when admitted to hospital, exhibit apparent incontinence of urine, careful examination and catheterisation will frequently show, in reality, the presence of an overflow incontinence, a considerable quantity of urine being retained in the bladder. Indeed, it is probable that in the majority of cases, retention of urine is the first manifestation of sphincter affection, leading, if untreated, to overflow incontinence. Retention usually accompanies stupor and the more profound stages of delirium, true paralytic incontinence as a rule only occurring with coma.

On admission to hospital, 50 per cent of cases over 14 years of age showed either retention, with some bladder distension, or apparent incontinence of urine. In the majority of patients exhibiting the latter symptom, percussion of the bladder region showed some dulness, and, on catheterisation, several ounces of urine were obtained. The usual mental condition accompanying this feature was either delirium or stupor ; retention of urine in the presence of an apparently normal mental condition was observed in two cases only. In this connection, it is interesting to note that urinary retention with normal consciousness may be the first physical sign of tuberculous meningitis.

The sphincters remain affected for a period varying with the progress of the case. In acute cases recovering after a comparatively short course (14 days or less), the initial retention or incon-

tinence usually persists for only a few days, improving *pari passu* with the mental condition. Retention, however, may persist for several days in some cases ; one patient, aged 32 years, whose cerebro-spinal fluid was quite clear and normal by the 14th day of illness, had exhibited retention of urine until the 10th day. Retention of urine, accompanied by occasional incontinence of faeces, persisted for 22 days in a youth aged 17, who recovered after a course of about 30 days' duration. In acute fatal cases, dying within 4-7 days, incontinence of urine and faeces is usually present from the time the patient first comes under observation until death. Fulminating cases are almost invariably incontinent, but often they die within such a short period that the sphincter condition is not noted.

Loss of control of the sphincters, not present at first, may occur later during the course. Thus, subacute cases terminating fatally become incontinent towards the end. When internal hydrocephalus develops, loss of control of the bladder and rectum often persists from the time of the appearance of symptoms due to this serious complication. Recrudescent cases may show a return of retention or incontinence, coincident with the recrudescence and following a period of normal control ; in a few cases, normal control or retention may have been present following the original onset of the disease, and incontinence occur only with the recrudescent attack ; the incontinence is usually accompanied by a marked change in the patient's mental condition, such as stupor or increased delirium. One patient, aged 15 years (Case XXII. p. 164), who exhibited several recrudescences during a course of 11½ weeks' duration, had retention with overflow when admitted to hospital on the third day of illness ; normal control was regained by the fifth day. Following this, he was incontinent only with the various recrudescences occurring between the 34th and 66th days of illness, no sphincter abnormality being present after the latter date.

A change in the character of the sphincter affection sometimes occurs. Thus, an acute case running a course of 31 days before terminating fatally, was admitted on the second day of illness with overflow retention. On the third day incontinence replaced the retention and continued until the 15th day ; from the 16th to the 28th days retention of urine occurred, incontinence reappearing on the 29th day and persisting until death.

When retention has been present for some days, incontinence of short duration may appear before normal control is regained. For instance, each of the two cases mentioned above as exhibiting

retention of urine from the time of admission to hospital until the 10th and 22nd day respectively, showed, on the disappearance of retention, urinary incontinence lasting about 48 hours.   Also, both patients complained of difficulty in restraining the precipitancy of micturition during the few days following the cessation of incontinence.

The cases we have classified as the progressively purulent type (*vide* Course, Chapter VII. p. 156) often show common features as regards the vesical sphincter.   Retention of urine appears somewhat late, usually about the 6th-8th day, and then persists ; the patient may, however, become incontinent shortly before death.   In two such cases, late retention was the first appearance of any sphincter affection ; other cases had had normal control for at least the preceding four days, any initial derangement of the sphincters having passed off within a day or two of admission to hospital.   Incontinence of faeces usually accompanies the late retention.

The incontinence of faeces which occasionally occurs during the performance of lumbar puncture or the intrathecal administration of serum is referred to elsewhere (*vide* Treatment, Chapter XVIII. p. 414).

Muscular Rigidity.—In association with the onset of the disease, there is frequently a complaint of pain in the limbs and particularly in the neck.   Following this pain, sooner or later, muscular rigidity develops in practically all cases ; it may be absent, however, in those of a fulminating type.

Rigidity of the Cervical Muscles.—Neck rigidity is absent in the early pre-meningitic stage of the disease, but occasionally slight pain may be experienced by the patient on flexing the head.   With the involvement of the meninges, however, rigidity of the posterior cervical muscles rapidly develops and is usually well marked by the time the case comes under observation.   In two cases admitted to hospital on the first day of illness and while the cerebro-spinal fluid was still clear and free from organisms (Cases II. and III. pp. 63 and 69), there was no suspicion of cervical rigidity in one, and, in the other, it was very slight, the chin just failing to reach the chest on flexion of the head.   Within 12 hours, however, distinct neck rigidity was present in both cases, and a turbid fluid yielding meningococci was obtained on lumbar puncture.

To ascertain the presence or absence of neck rigidity, we have found the following method most useful ; it constitutes a valuable sign in all forms of meningitis.   With the patient lying on his back,

PLATE III.

A. The Demonstration of Neck Rigidity.

The observer places his hand beneath the patient's head and endeavours gently to draw it forward. In the presence of meningitis, the head cannot be brought forward more than about 2 inches beyond the vertical line of the long axis of the body. More often, indeed, it cannot be flexed past this line (*vide* pp. 108-109).

B. Head Retraction.

A patient, aged 19 years, exhibiting head retraction on the fifth day of illness.

the observer places his hand beneath the head and endeavours gently to draw it forward. In the presence of meningitis, excepting occasionally in the tuberculous form, the head cannot be brought forward more than about two inches beyond the vertical line of the long axis of the body ; more often, indeed, it cannot be flexed past this line (Plate III. p. 108). In children, one can usually raise both head and trunk from the bed without flexion occurring at the neck. With manipulation of the head, true neck rigidity, as met with in meningitis, tends to increase, in contrast to that occurring in association with " muscular rheumatism," which tends to decrease.

During the course of the disease, the cervical rigidity varies from mere limitation of antero-posterior flexion of the head to extreme occipital retraction. It usually disappears during the coma that precedes death, and may be entirely absent in fulminating cases ; in the latter, death usually occurs before muscular rigidity has time to develop. In elderly patients, neck rigidity may also fail to appear, while Goeppert mentions a number of cases in young infants in which this symptom was absent throughout the course of disease. On the other hand, Heiman and Feldstein found cervical rigidity in 26 of 30 infants below the age of two years and suffering from cerebro-spinal fever. With the collapse that occasionally occurs at the onset of meningitis in acute cases other than fulminating, the development of neck rigidity may be delayed for a considerable time even in the presence of well-marked meningitis.

In our experience, cervical rigidity was present in 92 per cent of cases admitted to hospital with meningitis, as indicated by the withdrawal of turbid cerebro-spinal fluid on lumbar puncture. Among the exceptions, in addition to fulminating cases, are included two patients who were admitted in a deeply comatose condition on the third day of illness, each dying on the fourth and fifth day respectively without regaining consciousness. Another case, in which cerebro-spinal fever appeared immediately on recovery from bronchitis (Case XXVIII. p. 185), showed a sudden onset with rapid development of the disease. On admission to the isolation ward he was profoundly collapsed and exhibited a purpuric eruption but no neck rigidity ; the cerebro-spinal fluid was turbid and contained meningococci.

As neck rigidity increases, occipital retraction of the head may appear ; it is seen, however, with much greater frequency in children than in adults. In the posterior basic type of infants (vide Course, Chapter VII. p. 173), retraction is most marked, and

at times, in association with opisthotonus, the occiput almost
touches the sacrum. In adults, we have noticed that head retrac-
tion is more liable to occur in thin and spare subjects. When
present, it usually develops on the third or fourth day of illness in
adults and adolescents, but in young children it may appear earlier.
Of our adult cases, head retraction occurred at some time during
the course in 30 per cent. Some fatal cases showed the symptom
only during the last few days of life, and in other patients it only
occurred with the development of hydrocephalus. In a few cases
head retraction appeared about midway through courses of moderate
length (18-28 days), the patients recovering.

As a general rule, in cases terminating favourably, neck rigidity
gradually decreases and is quite absent within a few days of the
withdrawal for the first time of clear and sterile cerebro-spinal
fluid. In a few cases (5 per cent of our series), usually subacute,
the neck rigidity disappears shortly before the end of the course, *i.e.*
before the cerebro-spinal fluid becomes perfectly clear. Other cases
(10 per cent) continue to show neck rigidity for seven or eight days
after clear fluid is obtained, and in the absence of any symptoms
suggestive of hydrocephalus. Occasionally, the rigidity may per-
sist with definite head retraction well into convalescence, as in the
following case :

CASE XI.—An acute case, aged 19 years, was admitted on the second
day of a recrudescent attack of cerebro-spinal fever ; four days earlier
he had had an abortive attack at a local hospital. On admission,
considerable head retraction was present ; this symptom was still as
marked on the 24th day of illness, by which time the cerebro-spinal fluid
obtained on lumbar puncture was quite clear and sterile. At times
head retraction had been so extreme as to cause difficulty in swallowing.
One month after the termination of the course, the patient having
been up and about for over a week, there was still a tendency to retrac-
tion, with inability to bring the head quite into the vertical position
(*vide* Plate IV.). Massage, etc., was then instituted, and four weeks
later there was some improvement ; he remained, however, unable to
flex the head beyond the perpendicular while standing in the erect
position. Finally, it was not until 3½ further months had elapsed
(5½ months from the termination of the course of meningitis) that the
patient was able to flex the head sufficiently for the chin to reach the
chest.

With the general muscular relaxation during the coma that
usually precedes death, neck rigidity disappears.

The exact cause of cervical rigidity and of muscular rigidity in

PLATE IV.

HEAD RETRACTION PERSISTING INTO CONVALESCENCE.

The patient, aged 19, recovered from cerebro-spinal fever after a severe course lasting 24 days. The photograph shows the patient one month after the termination of the course of meningitis ; he is unable to flex his head beyond the position indicated.

general is somewhat uncertain. It is most probably produced by irritation, owing to the presence of inflammatory exudate, of the posterior roots of the spinal nerves, or possibly of the anterior horn cells. Increased tension of cerebro-spinal fluid apparently plays very little part in the production of rigidity in the cervical muscles, as the stiffness often remains unaffected after the withdrawal of considerable quantities of cerebro-spinal fluid. According to Cecil Wall, neck rigidity and head retraction may be produced as follows : In flexion and extension of the head, the cerebellum slides up and down the posterior surface of the medulla, folding and unfolding the arachnoid, which forms the bridge between them. If the arachnoid be inflamed, the posterior muscles of the neck contract to inhibit such movement.

Rigidity of the Spine.—In all cases, with the possible exception of those of the fulminating type, there exists some degree of rigidity of the extensor muscles of the spine. This rigidity appears very early, sometimes even before it is possible to demonstrate any definite neck rigidity. One of our orderlies, who had had considerable experience with the disease, could always offer a shrewd forecast as to diagnosis in a suspected case by the amount of resistance or otherwise offered to his efforts to bring the shoulders as near as possible to the knees, when holding patients in the requisite position for the performance of lumbar puncture. Not infrequently, spinal rigidity appears more marked in subacute cases than in acute, and the symptom tends to become more pronounced, as a rule, towards the fourth or fifth day, when a certain amount of backward arching may be present. In infants, and particularly in the posterior basic type, extreme opisthotonus may be a marked feature ; in some cases the head almost touches the sacrum. A certain degree of opisthotonus not infrequently accompanies internal hydrocephalus in adults as well as in children ; it may also be met with in patients running a somewhat long course quite apart from a hydrocephalic condition.

According to Busse, opisthotonus is associated with the fact that when the back is arched, the capacity of the subarachnoid space is increased ; this is borne out by the observation that flexion of the head and back during the performance of lumbar puncture accelerates the flow of cerebro-spinal fluid. In the majority of cases, however, no very marked diminution in the rigidity of the spinal muscles follows the removal of even considerable amounts of cerebro-spinal fluid ; consequently the actual cause of its production lies

probably in irritation of the spinal nerve-roots by inflammatory exudate.

Rigidity of the Limbs.—This symptom is frequently observed during the course of the disease, and in some cases it may persist for a short time after the termination of meningitis. In infants suffering from the posterior basic type of the disease, the limbs usually show a persistent stiffness, and the condition may simulate closely the characteristic attitude of tetany. In other children, the muscular contraction may be more spasmodic, and occasionally one may find firm palmar flexion of the thumbs with adduction of the fingers.

In cases exhibiting a long and severe course, an increasingly well-marked pes cavus is often observed in association with the general wasting, together with hyper-extension of the toes at the metatarso-phalangeal joints and flexion at the inter-phalangeal joints. One case, aged 15 years, showed this feature to an extreme degree on the 40th day of illness ; all movements of the toes were good, but the hallux could be hyperextended at the proximal joint to nearly a right angle.

Rigidity of other Muscles.—Retraction of the abdominal muscles may occur, causing the abdomen to assume a scaphoid appearance.

Trismus is observed occasionally but is rare. Distinct rigidity of the facial muscles often occurs in cases running a protracted course. In one patient, dying on the 31st day of illness, this rigidity frequently amounted to a definite risus sardonicus.

Kernig's Sign.—Dependent upon the symptom of muscular rigidity are certain signs of diagnostic importance. In addition to that of cervical rigidity, a sign of almost equal value is one first described by Kernig of Petrograd in 1884. His observation was but little known until 1898, when Netter drew attention to the supreme significance of Kernig's sign in the diagnosis of meningitis.

The test as originally described by Kernig is as follows : The patient, in bed, is propped up into a sitting position, the thighs forming a right angle with the abdomen. When the sign is positive, the legs will be found flexed at the knees, and owing to rigidity of the hamstring muscles, they cannot be extended completely until the back is lowered to form more than a right angle with the thighs. The method which gives the most constant results, however, and the one which we have most frequently employed, consists in placing and maintaining the thigh at right angles with the trunk, the patient lying in bed, while it is determined to what extent extension of the

leg, at the knee, is possible. Kernig's sign is then definitely present if the shank cannot be extended to within an angle of less than 45° of the vertical line of the thigh (*vide* Plate V. p. 114). In most normal individuals the leg can be almost fully extended, but some rigidity of the hamstrings may occur in conditions other than meningitis (*vide* Diagnosis, Chapter XII. p. 307). Another variation, less definite in its results, is the determination of the degree of angular flexion possible at the hip with the leg fully extended at the knee, after the manner of testing for Lasègue's sign in sciatica.

Kernig's sign is of no value in children below the age of two years, as at this age there often exists a physiological rigidity of the muscles which may yield a positive sign. Some authors state that it is a constant normal phenomenon below two years of age, but this is not so. As a matter of interest, in one infant with meningitis, aged 13 months, the sign was absent throughout a course of six days; in a second, aged four months, it was absent until the fourth day of illness, when it developed on the left side only, thus persisting until death on the 12th day. In another infant, aged seven months, Kernig's sign was positive on both sides throughout a course of eight days.

In the early stage of the disease, before the meninges have become involved, Kernig's sign is absent. Of four adult patients seen within 6-8 hours of the onset, the sign was negative in all; one showed a slight increase in rigidity of the hamstring muscles which was more marked on the right side than on the left. Two of these patients, on whom lumbar puncture was performed, yielded a clear cerebro-spinal fluid free both from organisms and from increase in the number of cells. Within eight hours, one patient had developed a purpuric eruption, but Kernig's sign was still absent and the cerebro-spinal clear and sterile; meningococci, however, were obtained from the blood-stream (Case II. p. 63). Nine hours later, Kernig's sign was well marked and a turbid fluid containing many meningococci was obtained on lumbar puncture. Of the three other cases, two showed a definite Kernig's sign within 12-18 hours, while in the last patient, owing to profound collapse occurring with the development of meningitis, and consequent muscular flaccidity, Kernig's sign was not present until the third day of illness. It would appear, however, that Kernig's sign develops before the cerebro-spinal fluid actually becomes turbid. For example, in a girl aged 13 years (Case IV. p. 70), and admitted early upon the second day of illness, Kernig's sign was just positive;

8

lumbar puncture yielded a clear cerebro-spinal fluid without relative increase in the number of cells, but containing numerous meningococci.

The following analysis of a series of 76 cases shows the incidence of a positive Kernig's sign in relation to the period at which the patient first comes under observation ; the majority of the cases were adults or adolescents, and all were over two years of age (patients seen on the first day of illness are not included).

Of 31 cases, excluding those of a fulminating type, seen on the second day of illness, Kernig's sign was definite in 27 and present, although not well marked, in three others.   In the remaining case it was absent ; this was a patient, aged 60 years, who was admitted on the previous day to a general ward, with a diagnosis of cerebral haemorrhage.   Coma, without preceding delirium, had suddenly supervened while he was waiting to see a medical officer.   When examined on the second day, he was stuporose, yet resentful of interference ; both legs could be raised to practically a right angle with the trunk and almost fully extended at the knees.   On the following day Kernig's sign was still absent, but he exhibited some rigidity of the hamstring muscles and the merest suggestion of stiffness in the neck ; lumbar puncture revealed a purulent cerebro-spinal fluid containing numerous meningococci.   On the fourth day Kernig's sign was well marked on the right side and less pronounced on the left.

Of 23 cases admitted to hospital on the 3rd day of illness, 21 showed a well-marked Kernig's sign ; in general, the sign was more pronounced than that seen in the second-day cases.   The two remaining cases were both comatose on admission and died within 34-48 hours.

Of 10 cases admitted on the fourth day of the disease, Kernig's sign was positive in all.

In 7 subacute cases, admitted on or between the 5th and 13th days of illness, Kernig's sign was well marked in five.   Of the remaining two, one showed the sign very slightly, while in the other, although there was some distinct rigidity of the hamstring muscles, it did not amount to a definite Kernig's sign ; a few days later, however, the sign was positive.

Of 5 fulminating cases, Kernig's sign was positive in one only.

From the above observations it is found that Kernig's sign is absent during the pre-meningitic stage of the disease, while the cerebro-spinal fluid is still normal.   Rigidity of the hamstring muscles usually begins within ten hours of the onset of the disease, and Kernig's sign is positive in 18-24 hours.   Also, as illustrated by Case IV., the sign may be present in association with an absence of meningeal exudate, that is, with a cerebro-spinal fluid clear to the

PLATE V.

KERNIG'S SIGN (Modified method).

With the patient lying in bed, the thigh is placed and maintained at right angles with the trunk, while it is determined to what extent extension of the leg at the knee is possible (*vide* p. 112).
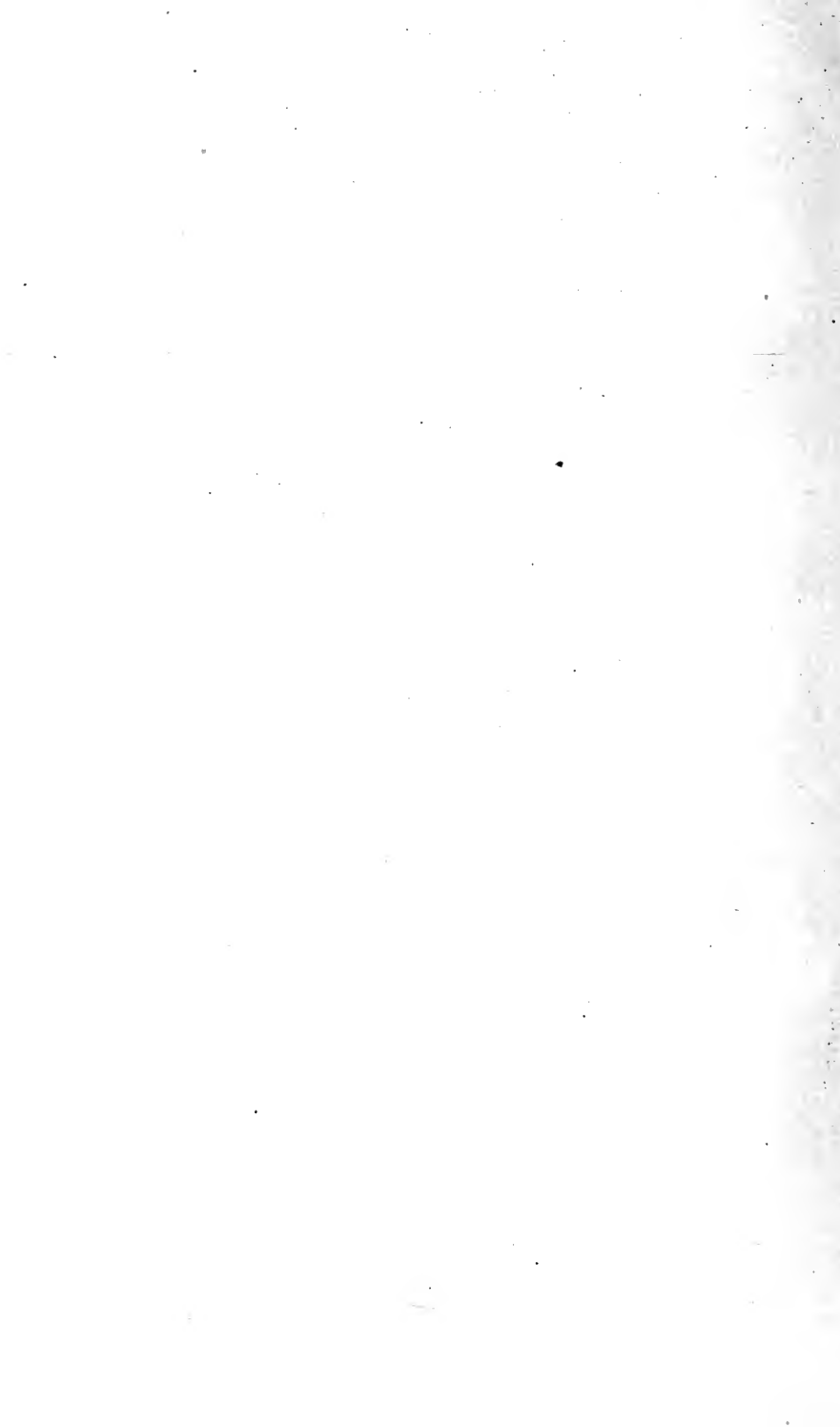
naked eye but containing meningococci. Of a total number of 80 cases of all types (including four cases seen on the first day of illness) and first coming under observation at different stages of the disease, Kernig's sign was positive in 68 (85 per cent) ; of 76 cases in which definite meningitis was present, the proportion exhibiting Kernig's sign was 89·5 per cent. The sign is usually absent in fulminating cases, and owing to the general muscular flaccidity, during the coma that precedes death. Also, it may not be present at the initial stage of meningitis if the development of the latter is accompanied by considerable collapse ; usually, however, if the patient survive this collapse, Kernig's sign develops later. In conclusion, it will be seen that, excluding fulminating cases and those seen shortly before death, Kernig's sign was present at some stage of the disease in all patients above the age of two years. The figure given by different authors as regards the incidence of Kernig's sign is that it is present in 90-95 per cent of cases with meningitis. It will be evident, however, from the observations above, that this figure will vary with the number of fulminating and comatose cases that are included.

Some observers have considered that Kernig's sign appears earlier than rigidity of the posterior cervical muscles ; this view arises, no doubt, because the former is more easily recognised than the latter. In our experience, however, some degree in limitation in flexion of the head is present some time before Kernig's sign is at all definite. It is true that slight rigidity of the hamstring muscles occurs practically coincidently with that of the neck muscles, but the latter can readily be demonstrated before the former amounts to a definite Kernig's sign ; this was the case in four patients received prior to the development of meningitis. In fatal cases, as coma deepens, neck rigidity frequently disappears before Kernig's sign.

The great majority of cases terminating favourably show a gradual increasingly well-marked Kernig's sign up to a certain point, usually the 5th-8th day ; it then remains constant for a time at about the same level, finally diminishing progressively towards the end of the course. In recrudescent cases, Kernig's sign may frequently be increased during the periods of crisis and diminished or absent during the intervals between them. Cases exhibiting a period of definite head retraction often show a Kernig's sign more pronounced during this period than preceding or following it.

Inequality of the sign on the two sides is occasionally observed. Of 76 cases, previously mentioned, on admission to hospital, Kernig's sign was distinctly greater on one side than on the other in five.

During the course, inequality occurred in ten cases, while in another, Kernig's sign persisted on the right side for four days after a normal cerebro-spinal fluid had been obtained, but was absent on the left. Of the 16 cases in which inequality was observed, the sign was more pronounced on the right side in thirteen, and on the left in three only.

As a general rule, Kernig's sign is the last symptom to disappear ; it usually persists for a variable period after the termination of meningitis, that is, after a cerebro-spinal fluid, sterile and normal in its cytological characters, is obtained for the first time, and there is no pyrexia or complicating hydrocephalus. In the majority of cases, Kernig's sign persists for the first 5-14 days of convalescence, but in a few of our cases it was still present 20 or even 30 days after the end of the course. Although the sign gradually disappears, some rigidity of the hamstrings can frequently be demonstrated 2-3 months after recovery. In a few cases (5 per cent) Kernig's sign disappears while the cerebro-spinal fluid is still turbid ; in one case recovering after a course of 30 days, the sign was not present after the 22nd day.

Many explanations have been advanced to account for the presence of Kernig's sign, but the most probable is as follows : In attempting to extend the leg, traction through the medium of the great sciatic nerve is applied to the spinal nerve-roots in the lumbar and sacral regions, and thence is transmitted to the spinal meninges. To inhibit this traction, a reflex contraction of the hamstring muscles occurs.

Brudzinski's Sign.—This sign was described in two modifications by Brudzinski in 1908 :

(*a*) The identical contralateral reflex. The patient lying supine with both legs extended, it is found that on flexing the leg and thigh of one side upon the abdomen, the other leg follows suit as soon as the flexed thigh touches the abdominal wall. If this reflex is absent the following may be elicited.

(*b*) The reciprocal contralateral reflex. One leg and thigh being flexed as before and the other extended, it is found that when the flexed leg is lowered to the extended position, the opposite limb undergoes, in turn, flexion on thigh and abdomen.

In 1909, Brudzinski described a further sign termed " la signe de la nuque " ; it is obtained by flexing the head of the patient on the trunk, the chest being held down by the observer's hand, when flexion at the hip and the knee also occurs.

Brudzinski states that he found the contralateral reflex in 66

per cent of cases, while Kernig's sign was present in only 57 per cent ;
the " signe de la nuque " was obtained in 97 per cent.   Morse, in
examining 400 children in normal health or with complaints other
than meningitis, did not meet with a single positive result.   Also,
Graeco was unable to detect Brudzinski's sign in conditions apart
from meningitis, while Zaimovsky found it almost constant in this
disease.

In our experience, the identical contralateral reflex was present
in a large proportion of cases (about 60 per cent of all types and at
all ages), and was more frequent in children and adolescents than in
adults.   We did not meet with a positive result, however, in any
case which failed to show a positive Kernig's sign.   The reciprocal
contralateral reflex we found present in only a few cases, and it was
of no diagnostic value.   The " signe de la nuque " was elicited in
about 80 per cent of cases ; frequently, in subacute cases coming
under observation after the third or fourth day of illness, retraction
of the head or extreme cervical rigidity effectually prevents any
flexion at the neck, and the sign cannot be elicited.   In early cases,
the neck sign is rather more frequently present than the contralateral
reflex.

Fairley and Stewart were able to test Brudzinski's contralateral
reflex in cases in which hemiplegia had supervened, the paralysis
being due to cerebral haemorrhage.   They found that on passive
flexion of the paralysed limb there was a marked contralateral
flexion on the sound side ; on passive flexion of the sound limb, no
movement of the paralysed limb occurred.

According to Brudzinski, the contralateral reflex is due to local
nuclear involvement, and he suggests that it is produced as follows :
There is a congenital tendency to bilateral innervation, an anatomical
connection existing between the nerve centres of corresponding
muscles on the two sides.   This is more definite and of longer per-
sistence in the legs than in the arms, on account of the slighter
differentiation of function in the former.   When the cerebrum is
diseased, especially in infancy and childhood, there is a tendency
for the specialised function to revert to the more primitive type.
The result of such a reversion is the presence of the contralateral
reflex.

The " signe de la nuque " is apparently dependent upon the
presence of muscular hypertonicity in the legs, together with physio-
logical predominance of the extensors of the neck and back over the
flexor muscles of the legs.

The Reflexes. *Knee and Ankle Jerks.*—These tendon reflexes are of no real diagnostic value in cerebro-spinal fever, and are of academic interest only ; they vary considerably with the state of consciousness of the patient, but as a rule the patellar reflexes and the ankle jerks are affected each to the same degree.

The following table of 51 cases shows the condition of these tendon reflexes in relation to the mental condition and the day of disease on which the patient was admitted to hospital.

TABLE III

Day of Disease on which the Patient was admitted.	Number of Patients.	Mental Condition.				
		Normal.	Drowsy.	Stupor.	Delirium.	Coma.
1st day (pre-meningitic stage) .	4	4 slight	...	...	...	...
1st day (meningitis present) .	2	...	...	2 slight	...	...
2nd day .	17	...	1 absent	...	...	3 absent
		...	...	5 slight	...	1 slight
		...	1 moderate	1 moderate	...	...
		2 brisk	...	...	2 brisk	...
		...	...	...	1 exaggerated	...
3rd day .	16	...	...	1 absent	1 absent	2 absent
		2 slight	...	...	1 slight	1 slight
		2 moderate	...	1 moderate	3 moderate	...
		2 brisk	...	...	...	...
4th day .	6	...	...	...	1 absent	...
		...	...	...	1 slight	1 slight
		...	...	...	3 moderate	...
After 4th day	6	...	...	...	1 absent	...
		1 slight	...	...	...	...
		1 moderate	...	...	3 moderate	...
Totals . .	51	...	1 absent	1 absent	3 absent	5 absent
		7 slight	...	7 slight	2 slight	3 slight
		3 moderate	1 moderate	2 moderate	9 moderate	...
		4 brisk	...	...	2 brisk	...
		...	...	...	1 exaggerated	...

In fatal cases, with the appearance of coma, the tendon reflexes gradually diminish and invariably disappear as coma deepens ; nine cases in which the tendon reflexes were elicited during delirium lost them as unconsciousness became more profound. In cases terminating fatally after a somewhat long course, these reflexes tend to become increasingly difficult to obtain throughout until finally they disappear.

The following observations relate to the condition of the knee and ankle jerks during the course in 34 cases recovering from the disease ; 15 patients showed a progressive increase of the deep reflexes from the day of admission until convalescence ; 4 only, in whom they were moderate on admission to hospital, showed a progressive diminution in response as recovery proceeded. Primary diminution followed by increase and again by decrease, was seen in 3 patients, with courses varying between 28 and 40 days ; the reverse—primary increase followed by diminution with secondary increase towards recovery—was observed in 6 cases.

Patients developing peripheral neuritis or a lower neurone paresis as a complication of the disease may lose the knee and ankle jerks (*vide* Complications, Chapter VIII. pp.199 and 202) ; apart from this, however, a few patients, owing to muscular weakness and hypotonicity, may exhibit absent tendon reflexes for a short period during convalescence.

Marked inequality in the knee and ankle jerks of the two sides, in the absence of complications of a paralytic nature, was observed in four cases of the 34 comprising the series on which these observations were made ; viz. two patients, on admission on the first and third day of illness respectively ; one, during the fourth week, and in the last, during the sixth week. Both the latter cases about this date showed symptoms of hydrocephalus. In all four patients the reflexes on the right side were the brisker.

Ankle Clonus.—True and definite ankle clonus, apart from upper neurone palsies occurring as complications, is rare. Of the 34 cases mentioned above it was observed in three only. In one subacute case, aged 25 years, who died of internal hydrocephalus on the 54th day of illness, left ankle clonus was present on admission to hospital on the 13th day ; it persisted with a few remissions until the 38th day, when double ankle clonus was obtained. With increasing drowsiness, however, it disappeared after the 49th day. The second case, also an adult, showed certain symptoms of hydrocephalus, becoming progressively drowsy, emaciated and tremulous ; on the 27th day, ankle clonus was obtained on the right side but not on the left. By the 38th day it had quite disappeared ; a few days later the patient had definitely recovered from meningitis.

Four cases showed merely a tendency to bilateral ankle clonus, on the second day in one case, from the third to sixth day in another, and during the second week in the remaining two cases.

Patellar clonus was obtained, on the 28th day, in one case only,

the patient mentioned above as showing hydrocephalic symptoms but recovering about the 40th day.

Oppenheim's Reflex.—This reflex is positive when contraction of the extensor proprius hallucis and tibialis anticus muscles occurs upon firm stroking along the postero-internal border of the tibia; its presence is said to be indicative of an upper neurone lesion.

In meningitis Oppenheim's reflex is most irregular and is of no diagnostic significance. Of 60 cases in which the reflex was sought, a positive result was obtained in three cases only. The first case, who showed a marked pes cavus with retraction of the toes, gave a bilateral extensor response on the fifth and sixth days of illness; that on the right disappeared on the seventh day, and that on the left a few days later. The second case exhibited a bilateral extensor response on the 20th day; from the 15th to 21st days the patient showed distinct symptoms of hydrocephalus. In the last patient, the reflex was confined to one side and was present only on the second day of illness. All three patients showed no other signs suggesting an upper neurone lesion, the knee jerks being moderate, plantar reflexes flexor and ankle clonus absent. Of 45 children over two years of age, Heiman and Feldstein found the reflex present in two cases only.

Interesting modifications were occasionally met with in other of our cases. One patient, aged 32 years, showed on the third day of illness, a homolateral flexor response and a contralateral extensor on each of the two sides. A second case, from the 7th to 14th days, gave a homolateral flexor and a contralateral extensor on the left side, but both a homolateral and a contralateral flexor response on the right; this was associated with a tendency to bilateral ankle clonus, but no other signs beyond somewhat exaggerated knee jerks.

Gordon's Paradoxical Reflex.—This reflex consists in extension of the hallux or of all the toes when deep pressure is applied to the muscles of the calf. It is indicative of an upper neurone lesion, and its author claims that it is often present before either Babinski's sign or Oppenheim's reflex develops.

We obtained a positive result in two cases only, on the second and 15th day of illness in each respectively; it was unassociated with any other signs of upper neurone interference.

Plantar Reflexes.—In the majority of cases, when a complicating upper neurone paresis is absent, the plantar reflexes are flexor,

Babinski's sign being absent. Fifty-six cases above the age of two years, and exhibiting no paralytic complications, were examined on numerous occasions throughout the course of disease ; the plantar reflexes, when elicited, were invariably flexor in all cases excepting seven. These seven instances occurred as follows :

A subacute case when admitted on the third day of illness exhibited a bilateral extensor reflex (Babinski's sign) ; on the 6th day the reflex on the right only was extensor, that on the left being flexor ; after this date both became and remained flexor.

A second case gave a bilateral extensor response on the 6th and 7th days of an acute attack lasting 10 days.

In 2 acute fatal cases, each dying on the 4th day of illness, extensor plantar reflexes were obtained on the 3rd day, prior to the supervention of coma.

In the remaining 3 cases the extensor reflex was only unilateral.

A case seen within 24 hours of the onset, but yielding a turbid cerebro-spinal fluid, gave a definite extensor plantar response on the right side, while on the left a very slight flexor movement of the hallux was followed by marked extension. Both reflexes were flexor when examined on the 4th day, and so remained during the subsequent course.

In 2 further cases, both acute, an extensor response was present on the 3rd and 4th day respectively ; in each case it was confined to the right side.

A much reduced flexor response is occasionally seen in comatose cases ; it completely disappears as death approaches. In one case, which was more or less delirious throughout the course of illness and proved fatal on the 31st day, a reduced flexor reflex was obtained until the 26th day, being followed by complete absence until death. Crossed bilateral flexor responses may also be met with ; one patient exhibited on the 12th and 14th days a homolateral flexor with a contralateral extensor reflex on the left and a crossed flexor on the right ; this was associated with a similar Oppenheim's reflex.

A sign, often of some diagnostic value, consists in active withdrawal of the leg by the patient on an attempt being made to elicit the plantar reflex ; this is associated with the general irritability and hyperaesthesia. It was present, on admission to hospital, in 38 of a series of 60 consecutive cases ; the accompanying mental condition was usually one of stupor or delirium.

Abdominal Reflexes.—These reflexes vary considerably with the state of consciousness of the patient. In coma, they are almost

always absent and frequently also in stuporose patients.   In cases
profoundly delirious they are usually much reduced.

The following summary shows the condition of the abdominal
reflexes in a series of 41 consecutive cases :

In 19 cases they remained present throughout the course of the
disease ; although in 14 of these cases, the reflexes were considerably
reduced when the patient was admitted to hospital, they increased
later as the case improved. Of the 19 cases, in 15 the mental condition
varied from occasional delirium to stupor ; in the remaining 4 con-
sciousness was normal.

In 5 cases moderately brisk abdominal reflexes were elicited on
admission ; during the course, however, they disappeared for a period
varying in different patients, but reappeared later with progress towards
recovery. In each case their disappearance was associated with a
change in the patient's mental condition—increased delirium or de-
lirium changing to stupor in 3 cases and extreme drowsiness together
with hydrocephalic symptoms in the other 2.

In 5 cases the abdominal reflexes were unobtainable on admission,
but appeared subsequently with improvement in the patient's general
condition.

In 6 fatal cases the abdominal reflexes were present on the patient's
admission to hospital but disappeared as the patient became more
profoundly unconscious a day or two before death.

In 6 cases, also proving fatal within 5-10 days of the onset, complete
absence of the abdominal reflexes was observed throughout the course
of illness.

Taken in conjunction with other signs, the absence of the
abdominal reflexes rather favours a diagnosis of meningitis, and
their persistence or otherwise is of some prognostic value.   When
hemiplegia occurs as a complication, the reflex may disappear on
the affected side, while that on the normal side persists.

Cremasteric Reflexes.—These reflexes are usually more or less
proportional to the abdominal reflexes and call for no special com-
ment beyond the fact that owing to a contracted condition of the
scrotum often observed during the course of the disease, they are
sometimes unobtainable when the abdominal reflexes are well
marked.

Cranial Nerves.—*Pupils.*—During the early stage of the disease
the pupils are usually dilated and respond sluggishly to light.   In
a few acute cases, however, they appear contracted.   According to
Horder, mydriasis may sometimes be noticed to increase when the
head is tilted forwards or during the demonstration of Kernig's

sign ; this would be accounted for by the fact that sudden pain, which is known to produce reflex pupillary dilatation, is caused by the stretching of the somewhat rigid muscles. In the presence of hydrocephalus, the pupils are frequently widely dilated and occasionally irregular. Inequality in the size of the two pupils is somewhat infrequent ; we have only observed it in acute cases proving fatal or associated with hydrocephalus ; in the former, the inequality often persists after death.

Optic Discs.—In cerebro-spinal fever, definite optic neuritis is distinctly more uncommon than in other forms of meningitis ; possibly its appearance may vary in different epidemics, as different observers do not agree in their views regarding its frequency. This difference of opinion is illustrated by the following table :

TABLE IV

Authors.	Number of cases examined.	Number of cases exhibiting optic neuritis.	Percentage.
Travers Smith	36	nil	0
Matthes	35	nil	0
Foster and Gaskell . . .	30	1	3
Heine	160	8	5
Ballantyne	61	5	8
Uhthoff	160	18	11
Randolph	40	6	15
Fairley and Stewart . . .	184	76	41

Of our own cases definite optic neuritis was found in only five patients of 80 examined (6·25 per cent) ; four of the cases were subacute. In the acute case, optic neuritis was discovered on the eighth day of illness. It was present on the sixth day in one subacute case and on the 12th day in two ; in the last case, who recovered after a course of 30 days' duration, optic neuritis was first observed on the 14th day of illness and was followed later by haemorrhage into the vitreous (*vide* Chapter VIII. p. 206). In four of the cases the optic neuritis was associated with strabismus.

At the height of the disease in acute cases, and also in those developing hydrocephalus, some hyperaemia of the optic discs, with occasional blurring of the nasal margin, may sometimes be observed but is of no value in estimating prognosis.

In 184 cases, Fairley and Stewart give the following results of a routine examination of the optic discs by Gault :

69 cases showed double optic neuritis.
 7   ,,   ,,   unilateral optic neuritis.
 3   ,,   ,,   optic neuritis of one disc with hyperaemia of the other.
35   ,,   ,,   hyperaemia only.
 1   case   ,,   unilateral hyperaemia.
 1   ,,   ,,   pallor of discs.

Primary optic atrophy is said to occur but is very rare. In the posterior basic type of infants, blindness of central origin may develop (*vide* Complications, Chapter VIII. p. 207); changes in the optic discs are rarely seen but a few cases show a secondary optic atrophy.

Strabismus.—Disturbances of the extrinsic muscles of the eyeball are often observed in cerebro-spinal fever, but their appearance is not nearly so constant as in tuberculous meningitis. From time to time the strabismus may vary, and it seldom amounts to definite paralysis of the affected muscle. In adults, especially subacute cases, a complaint of diplopia on looking sideways without demonstrable oculo-motor lesion is not infrequent. Strabismus, when present, is usually divergent, and if paresis occurs, the sixth nerve, no doubt owing to its relatively long intracranial course, is the nerve most often involved. We were able to demonstrate weakness of one or more of the rectus muscles in 23 of 118 cases (19·5 per cent). In three adolescents, both sixth nerves were involved and led to paralysis of both external recti; in two of these cases, the ocular movements were normal within 10 and 25 days respectively of the appearance of the lesion, but in the remaining case paralysis was still present five weeks after recovery. In another case, there was apparent paresis of both superior recti.

As a rule, strabismus appears within the first four or five days of illness, but in cases developing some degree of hydrocephalus, it may appear only with this complication (*vide* Chapter IX. p. 223). Usually, strabismus disappears before or within a few days of the termination of the course. In cases proving fatal, deviation of one or other eye may occasionally be observed during coma.

Ptosis.—Ptosis may occasionally occur. Of our cases it was observed in three, being present on the third day in two cases and on the fifth in one; all the patients recovered, the ptosis having disappeared by the 12th day of illness. Two of the patients also exhibited a divergent strabismus. Of 410 cases H. D. Rolleston mentions the occurrence of ptosis in 15, 11 of which proved fatal (73·3 per cent).

Nystagmus.—This condition is sometimes present, especially in association with internal hydrocephalus. Apart from this serious complication, nystagmus was observed in four only of our patients ; in three cases it occurred before the fifth day. The last, that of a patient aged 13 years, showed nystagmus on the second day of illness ; it persisted until the 18th day, and from the 12th day onwards was associated with paresis of both external rectus muscles.

Exophthalmos.—Some degree of exophthalmos may appear in cases developing internal hydrocephalus and particularly in that complicating the posterior basic type of the disease ; in the latter, the eyes are often seen turned downwards, the sclerotics being exposed by retraction of the upper lids.

One patient, aged 17 years, and recovering after a meningitic course of about four weeks' duration, showed evident symptoms of hydrocephalus from the fifteenth to the 20th day ; during this period, a weakness of the left external rectus muscle, previously present, developed into definite paralysis. The pupils were widely dilated and there was a marked tendency to exophthalmos, von Graefe's sign being positive. Upon the frequency of lumbar puncture being increased from once to twice daily, these symptoms rapidly passed off.

Trismus occurs occasionally but is rare.

Facial Paralysis.—A transient facial paralysis may be observed. It was present in two of our cases, appearing on the third and fourth day of illness in the respective cases, and disappearing during the second week. Rigidity of the facial muscles has already been mentioned (p. 112).

Inability to swallow is present during coma, but patients delirious or stuporose usually swallow their feeds fairly well.

Transient Aphonia has been recorded but is rare.

Hypoglossal Nerve.—The 12th nerve, as shown by deviation of the tongue on protrusion, may occasionally be affected. In one of Foster and Gaskell's cases, deviation of the tongue was observed, together with facial paralysis and internal strabismus ; all these symptoms passed off within a month.

Deafness is considered among the complications of the disease (Chapter VIII. p. 208).

Sensory Disturbances. *Hyperaesthesia.* — Hyperaesthesia to touch is almost an invariable symptom in the earlier stages of the disease. In infants, it may be a premonitory symptom, and Goeppert states that he was enabled to make an early diagnosis in

several cases by this symptom alone. Associated with the hyper-aesthesia, intense irritability may be present in delirious and stuporose patients, as shown, for instance, by the active and immediate withdrawal of the leg when an attempt is made to elicit the plantar reflex; this active withdrawal of the leg was observed, on admission to hospital, in 30 of a series of 56 consecutive cases.

In hydrocephalic cases, general hyperaesthesia is often pronounced. One subacute case developing hydrocephalus showed cutaneous hyperaesthesia of the legs only; in several cases the hyperaesthesia was more marked along the spine.

Pain.—In addition to headache, which has already been dealt with (p. 75), there is often considerable pain experienced in the limbs, back and neck; during the course of the disease, spontaneous pains in the arms and the legs may also occur. Sheffield Neave mentions three cases complaining of severe pain on both sides of the chest and two with pain in the abdomen, as if corresponding in distribution to definite spinal nerves. Also, Netter refers to the occurrence of severe sciatic pain which may persist into convalescence.

One of our subacute cases, on the 12th day of illness, complained of intense pain around the shoulders; on examination, a bilateral area of hyperalgesia was mapped out across the back and extending on to the inner aspects of the arms, roughly corresponding to the area of distribution of the posterior primary divisions of the second thoracic nerves. A second patient, complaining of pain in both scapular regions, showed a similar condition in the area of the fourth and fifth thoracic nerves.

It is probable, as Netter and Debré suggest, that sensory phenomena are due to irritation of posterior nerve roots, and in the production of which the tension of the cerebro-spinal fluid may play some part. Certainly in some cases, we have noticed that hyperalgesia along the spine is considerably relieved by the withdrawal of several c.cms. of cerebro-spinal fluid.

Photophobia.—As compared with its frequency in tuberculous, pneumococcal and streptococcal meningitis, photophobia is not altogether a common symptom in cerebro-spinal fever. It may be present in very acute cases, but, on the whole, we have observed it in relatively few patients. In a series of 410 cases, commented upon by H. D. Rolleston, photophobia was noted in 42 (10·2 per cent).

In a few cases, comparatively late in the course, there may be a complaint of severe pain behind the eyes.

Motor Disturbances.—*Floccitation and Carphology.*—Floccitation (picking movements, *e.g.* at the bed-clothes) and carphology (a movement of the hands in front of the face as if gathering imaginary objects) are most frequently present in acute cases and are of somewhat grave import ; of nine cases in which these symptoms were observed, only two recovered. The presence of floccitation and carphology probably depends upon irritation of the cerebral cortex by the upward spread of infection. In those cases exhibiting floccitation which came to autopsy, purulent exudate was invariably found on the upper or lateral aspects of the cerebrum, either along the courses of the blood vessels or spread on each side of the great longitudinal sinus.

Tremors, etc.—Tremors and rhythmical movements affecting various muscle groups may often be observed. A tremor of the hands frequently occurs both in children and in adults from the earliest stage of the disease. The following conditions were also noted in our series of cases :

A continuous tremor of the arms was present in one case admitted on the third day of illness ; the patient was delirious at times, but during the intervals of lucidity answered questions quite well. He proved, however, to be a progressively purulent type of case (*vide* p. 156), and died on the tenth day of illness.

Spasmodic twitching of the extremities and sometimes of the head was occasionally observed late in the disease in cases proving fatal. Spasmodic head-shaking from side to side occurred on the 15th day in a recrudescent case aged 5 years and dying on the 18th day of disease.

Fine tremors of the lower jaw were observed in two cases, on the second and third days of illness in an acute case terminating fatally on the fifth day, and in the later stages of one dying on the 31st day.

Teeth-grinding occurred in an acute case admitted on the second day of illness in a state of stupor with intense irritability.

Twitching of the eyelids and also of the hamstring muscles was observed in a few cases when the patient was lying quite undisturbed.

Attacks of trembling, often lasting an hour and unassociated with any change in temperature, occurred in a hydrocephalic patient at intervals from about the 30th to the 48th day of illness ; the case proved fatal on the 54th day.

Progressively increasing tremulousness is often seen in associa-

tion with hydrocephalus ; cases exhibiting this tremulousness do not necessarily prove fatal.

Convulsive Seizures. — Generalised convulsions are comparatively common in infants and young children but rare in adults. In infants, the disease is frequently ushered in by a convulsion, and during the course such seizures may recur ; one infant, aged four months and in whom convulsions occurred at the onset, exhibited similar disturbances throughout a course terminating fatally after eight days. Another infant, aged three months, showed as many as 15 convulsions in one day.

Of adults, a convulsive seizure may occur occasionally in very acute cases ; for instance, a fulminating case dying within 36 hours of the onset, was stated to have had a convulsion shortly before death. A case of the progressively purulent type, dying on the ninth day, exhibited a convulsive attack as follows :

CASE XII.—The patient, aged 24 years, was admitted to hospital acutely ill on the third day of disease. During the first few days of observation, he showed signs of improving, but following this, the cerebrospinal fluid gradually became increasingly thicker and more difficult to obtain. Delirium, incoherency and hallucinations ensued on the seventh day. On the ninth day, after being washed, the patient suddenly became cyanosed and appeared quite unconscious ; the corneal reflex was absent, and within a few seconds, he developed general clonic movements of a typical epileptiform nature. The seizure lasted about three minutes, and following its cessation the patient remained cyanosed and unconscious ; the corneal reflex, however, was now sluggish. Neck rigidity appeared less marked than before and the pulse was very feeble. Throughout the seizure the plantar reflexes when present were found to be flexor. On lumbar puncture, about 15 c.c. of very thick purulent fluid were obtained ; following this evacuation the patient's condition improved, as he protruded his tongue when asked to do so. About eight hours later he relapsed into coma, the limbs becoming flaccid and all reflexes, including the corneal, disappearing. Death occurred five hours later, that is 13 hours after the seizure.

With gradually increasing hydrocephalus, clonic and tonic spasms may occur. In hydrocephalic children, convulsions are relatively common, and in adults they may also be observed. In one case, aged 25 years, who developed internal hydrocephalus, we were able to witness a convulsive seizure occurring as a terminal symptom (Case XLV. p. 225).

From this patient, during the preceding few days, small quantities only of cerebro-spinal fluid had been obtainable. On the morning of

the 54th day, no fluid whatever escaped through the lumbar puncture needle in spite of the fact that three intervertebral spaces were entered. During the afternoon, the patient's respiration was noticed to be somewhat laboured, when quite suddenly his head became more retracted ; this was followed by opisthotonus, cyanosis, and external deviation of the left eye. Thus the patient remained for about two minutes, scarcely breathing ; upon the administration of oxygen, there occurred clonic movements at the large joints (hips and shoulders), the hands and feet being in tonic contraction. This seizure, in turn, was succeeded by a fit of general trembling, lasting about four minutes. Four hours later the patient died without regaining consciousness.

Paroxysmal tetanus-like seizures, with spasmodic retraction of the head and rigid extension of the arms, have been described in rare instances. Cases exhibiting such symptoms early in the disease have occasionally been mistaken for cases of true tetanus.

In adults, convulsive seizures are usually manifestations of either a meningo-encephalitis or internal hydrocephalus ; one or other of these conditions is almost invariably found post mortem. When such seizures occur, therefore, the prognosis is extremely grave.

When epileptiform attacks are observed in comparatively mild cases, the possibility of true epilepsy must be borne in mind and an inquiry made into the patient's previous history. In Fairley and Stewart's series of cases, of eight patients exhibiting convulsions, the only two who recovered were epileptics.

Other motor disturbances, in the form of muscular rigidities and lesions of the cranial nerves, have previously been described (pp. 108-125). Paralyses affecting the limbs are considered among the complications of the disease (Chapter VIII. p. 197).

Disturbances of the Vaso-motor System.—Instability of the vaso-motor system is observed in all cases. Tache cérébrale is invariably well marked, but is of no diagnostic value as it is by no means confined to cerebro-spinal fever or meningitis. The tache appears rapidly and is usually of great intensity and persistence. It may often be elicited months after convalescence. Further evidence of vaso-motor change is indicated by the frequent presence of alternate flushing and pallor.

Spontaneous flushing in different parts of the skin may occur, and, also, irregularities of perspiration. Evanescent localised erythema is frequently seen ; the points of pressure over bony parts become very reddened and may lead to sores.

Priapism is occasionally observed.

It has been suggested by Netter and Debré that the vaso-motor instability is due to irritation of the floor of the fourth ventricle, the ependymal lining of which frequently shows marked changes. More probably, however, it is a result of asthenia, as a tache cérébrale can be elicited in most cases of neurasthenia and other conditions in which the nervous system is depressed.

Trophic Disturbances.—*Wasting.*—In practically all cases, after the first five or six days, wasting occurs with such constancy as to constitute a characteristic feature of the disease. In cases continuing for long courses, and particularly in those complicated by hydrocephalus, the progressive emaciation may reach an extreme degree. Cases recovering, however, gain flesh rapidly during convalescence.

It is probable that the wasting is due to a disturbance of the normal trophic influences originating in the central nervous system. In support of this view, it may be remarked that wasting is present in all cases not proving fatal within the first week ; in the great majority, it is seen quite apart from vomiting or diarrhoea, and, in many cases, the patient is taking liberal nourishment. The disturbance may arise from interference with the anterior horn cells of the spinal cord or with the anterior spinal roots ; probably, however, changes in the cerebral cortex, the flattening of the convolutions, etc., by meningeal exudate or by pressure from within the ventricles (internal hydrocephalus), play a more important part.

Bed-sores.—Bed-sores are very liable to occur, not only on the back and hips but also on other points of pressure, such as the outer sides of the knees, malleoli and elbows. Unless care be taken to prevent these lesions, they may become extensive and form sloughs.

Generalised Hydrocephalus.—In meningitis, two varieties of hydrocephalus are met with : (*a*) Generalised hydrocephalus, and (*b*) Internal hydrocephalus. The latter condition is considered as a complication and is fully described in the chapter dealing with hydrocephalus (Chapter IX. p. 219).

The term " generalised hydrocephalus " is applied to that type of hydrocephalus in which there is considerable accumulation of cerebro-spinal fluid under increased tension, not only in the ventricles, but also throughout the subarachnoid space. In contrast to the condition obtaining in " internal hydrocephalus," there is no occlusion, partial or complete, of the outlets of the ventricular system.

In the early stages of meningitis, generalised hydrocephalus is

almost invariably present and is responsible for such symptoms as persistent headache, vomiting, stupor and, in children, bulging of the anterior fontanelle. In older children Macewen's sign (*vide* p. 132) may often be found, but is much less constant than in internal hydrocephalus. Generalised hydrocephalus is relieved by frequent lumbar puncture, and many cases show considerable improvement even after one such operation. The cerebro-spinal fluid is almost always found under increased pressure.

The following case is an example of generalised hydrocephalus occurring early in the disease and yielding rapidly to lumbar puncture :

CASE XIII.—The patient, aged 19 years, felt quite well during the morning of the day of onset ; towards evening, however, he complained of dizziness and headache. The latter symptom increased in severity and later vomiting occurred. On going to bed, the patient failed to fall asleep until 2 A.M., and from this point onwards was unable to remember anything that occurred until the following evening, when the above history was obtained.

When admitted to hospital on the morning following the day of onset, the patient was quite stuporose and lay apparently unconscious but resenting interference. The temperature was 101° F., pulse 72, and respirations 22 ; neck rigidity, Kernig's sign and Brudzinski's sign were all present. The pupils were slightly dilated but reacted sluggishly to light, and, on attempting to elicit the plantar reflex, the leg was actively withdrawn. On lumbar puncture, 60 c.c. of turbid fluid under greatly increased pressure were obtained ; microscopical examination showed numerous polymorphonuclear cells and a few mononuclears but no organisms. In culture, however, a good growth of meningococci developed.

Following lumbar puncture, the patient was much more conscious and, at intervals, answered questions in a vague manner. During the evening, however, he was able to give the history of onset.

Next morning the general signs of meningitis were unchanged, but consciousness was practically normal. Head retraction was very marked from the 3rd to 6th day ; nevertheless the patient made a rapid and uninterrupted recovery, the temperature being normal and the cerebro-spinal fluid perfectly clear by the 7th day of illness.

Treatment consisted of lumbar puncture combined with the intra-thecal administration of serum for the first four days ; following this three further daily lumbar punctures were performed, until a clear and normal cerebro-spinal fluid was obtained (7th day). Two doses of polyvalent vaccine were also given (250 and 500 millions respectively) on the 2nd and 6th days in hospital.

In addition to that present in the early stages of meningitis,

generalised hydrocephalus may appear, subsequent to the first week, at almost any time during the course of the disease. Such an occurrence is considered in the special section dealing with hydrocephalus (Chapter IX. p. 212).

The condition of generalised hydrocephalus is due to the increased production of cerebro-spinal fluid by the hyperaemic choroid plexuses ; decreased absorption by the pia-arachnoid, owing to its being covered with inflammatory exudate, has also been considered a causative factor. The work of Hohn, Levy and Flexner on the ready absorbability of antimeningococcal serum suggests, however, that there is no marked interference with the absorptive functions of the lining of the subarachnoid space.

The Cranium.—*Fontanelles.*—In young children, the anterior fontanelle is often found tense and bulging in the early stage of meningitis owing to the presence of generalised hydrocephalus. During the third week, however, it may become depressed, even in cases terminating fatally. Crying causes the tension of the fontanelle to become more pronounced, and occasionally regular pulsation may be felt.

With a considerable increase in intracranial pressure in infants, the posterior fontanelle may sometimes reopen.

Sutures.—Associated with bulging of the anterior fontanelle, there is not infrequently some separation of the cranial sutures ; Goeppert found this condition in 13 of 34 cases. In hydrocephalic infants, on account of this separation, the head may become distinctly enlarged.

Macewen's Sign.—In adolescents and children with closed fontanelles, even a moderate amount of hydrocephalus may frequently be demonstrated by means of Macewen's sign. This sign is present when a dull tympanitic note is elicited by percussion of the skull in the fronto-parietal region. It is best obtained by tilting the head slightly towards the side to be tested, and then percussing firmly over the skull with the finger, either directly or upon the finger of the other hand. If the percussion note thus produced in a hydrocephalic case be compared with that in a normal individual, the difference is striking, and soon dispels any doubt that may exist as to the value of the sign. In Heiman and Feldstein's cases, Macewen's sign was present in 35 of 45 children above the age of two years. We have occasionally elicited the sign in adults, but, as a rule, the thickness of the skull renders it uncertain.

Macewen's sign is due to an increased amount of fluid within the

ventricles ; consequently it is more constant in internal hydrocephalus than in the generalised form.

Dilatation of Veins.—In well-marked internal hydrocephalus, as seen, for instance, in the posterior basic type of infants, the superficial veins of the scalp may become dilated and very prominent, especially over the temporal region.

CHAPTER VII

COURSE

THE course of illness in cerebro-spinal fever varies considerably with the particular type of the disease. Certain features, however, may be considered from a more general standpoint.

Following the onset, the first day is usually marked by the further development of cerebral symptoms; on the second day there is not infrequently some apparent improvement. It is important to recognise this in order not to lose the opportunity of early treatment; some degree of neck rigidity will almost always be apparent together with a positive Kernig's sign.

An appreciable and often considerable fall in the temperature almost invariably follows the first lumbar puncture; in many cases, there is also some improvement in the patient's general condition. Nevertheless, serum treatment must not be withheld on this account, as such improvement is merely temporary; it is essential, therefore, to adopt the rule of administering serum intrathecally for at least four days, however mild the case may appear.

According to the course taken by the disease, we have classified cases as follows:

A. **Acute Types—**
    (1) Fulminating type (death within 48 hours).
    (2) Acute fatal type (death within 4-7 days).
    (3) Acute cases which recover after a short course (8-14 days).
    (4) Acute cases running a long course (20-30 days).
    (5) Acute cases which become subacute.
    (6) Abortive type (2-4 days).

B. **Special Types** (originally acute or subacute)—
    (1) Progressively purulent type (death usually occurs in from 9 to 20 days).
    (2) Recrudescent type. (Duration of course varies from 14 days to several weeks or even months.)

C. **Subacute Types—**
   (1) Mild cases (6-9 days).
   (2) Moderately severe cases : (*a*) Short course (under 15 days).   (*b*) Longer course (over 15 days).
D. **Chronic Types** (originally acute or subacute)—
   (1) Ordinary chronic type (6 weeks to several months).
   (2) Posterior basic type of infants.
E. **Relapses.**

For the purpose of definitiveness, we have estimated the length of the course, in cases recovering, as from the day of onset of disease until the day on which normal cerebro-spinal fluid, on lumbar puncture, is obtained for the first time, all pyrexia or evidence of hydrocephalus being absent.

ACUTE TYPES

Fulminating Type. — The term fulminating, foudroyant or malignant, is applied to those cases commencing abruptly and rapidly proving fatal within 24 to 48 hours of the onset ; they are frequently met with early in an epidemic. It is this type of the disease in which the purpuric eruption is most often seen, and that has produced in the lay mind the dread associated with the name of " spotted fever."

The onset is almost invariably sudden, the patient having made no previous complaint of ill-health ; one or more rigors may occur, followed by intense headache. Vomiting is sometimes present but is frequently absent. Delirium rapidly makes its appearance, as a rule, within a few hours of the onset, and the patient may often become very violent or even maniacal ; at other times, the period of the duration of delirium is brief. Coma eventually supervenes in all cases, and the patient dies in 48 hours or less of the first appearance of symptoms. In some cases, coma follows almost immediately upon the onset ; individuals have gone to bed apparently in their ordinary health, and have been found unconscious or even dead on the following morning. One of our patients, having undergone riding instruction during the morning, was found comatose in his hut late in the afternoon ; death occurred within 24 hours.

A purpuric rash, appearing within a few hours of the onset, is usually present, the blotches (vibices) varying in size from that of a pea to that of a plum. They are scattered somewhat indiscriminately over the body, but as a rule are rather more plentiful about

the hips and extensor surfaces of the limbs ; they may occur, however, even on the face. Many petechiae are also present, being conspicuous at the points of pressure ; in some cases the purpuric spots are absent, a petechial rash alone being visible.

As regards general aspect, the patient may either appear pale and intensely collapsed, or cyanotic and bathed in perspiration. If seen early, delirium may be present, but most cases are comatose by the time they come under observation. We have found the temperature somewhat variable in different cases; not infrequently, it is but little raised (99°-100° F.), but in some cases it remains between 100° and 103° (Fig. 15) ; in others the temperature is subnormal. The pulse is feeble and fluttering (120-140), and may occasionally appear irregular owing to some of the weak cardiac beats failing to be transmitted to the wrist ; some right-sided cardiac dilation can frequently be made out. The respirations are rapid and shallow, and urgent dyspnoea is frequent ; towards the end, breathing of the Cheyne-Stokes type may occur. Neck rigidity is usually absent or very slight ; midway through the course, a positive Kernig's sign may be elicited, but with coma of increasing depth it soon disappears. Occasionally, as with one of our fulminating cases, a convulsive seizure may occur prior to death.

Date				
Day of Dis.				
Time		AM	PM	
		2 6 10 2	6 10 2	

Temperature (Fahrenheit)
106°
105°
104°
103°
102°
101°
100°
99°
Normal 98°
97°

Pulse	M	120	110	140
	E	124	110	?
Resp	M	26	26	46
	E	24	24	56

FIG. 15.—Fulminating type. Case apparently well at midday but found unconscious at 6 P.M. Death within 36 hours of onset.

The following case illustrates the fulminating type of the disease :

CASE XIV. (*Fulminating Type*).—A soldier, aged 18, had been feeling perfectly well until one afternoon he felt " chilly " ; soon after, he complained of headache and abdominal pain, and within an hour or two vomited. He was admitted to hospital comatose ; a petechial rash was present on the legs and to some extent on the posterior aspect of the body. Several purpuric patches were also seen on the hips and extensor surfaces of the arms. The temperature was 100° F., pulse 120, respirations 46 and stertorous ; there was no neck rigidity, and Kernig's sign was absent, there being merely slight rigidity of the hamstring

muscles. Lumbar puncture yielded 60 c.c. of slightly turbid fluid under increased pressure and showing, on direct microscopical examination, moderate numbers of meningococci, both intracellular and extracellular. His condition showed no improvement following lumbar puncture and serum administration, and he died a few hours later without regaining consciousness.

A fulminating course may occur in infants as well as in older children and adults, but is not often diagnosed prior to death.

There is every reason for believing, as we have already shown (Chapter V.), that the mode of entry of the meningococcus to the meninges in cerebro-spinal fever consists in the absorption of the organism from the naso-pharynx into the circulation, through the medium of which it is carried to its site of election, the meninges. In fulminating cases, the whole aspect is usually that of a profound toxaemia, and most probably there occurs a definite and intense infection of the blood, constituting a true septicaemia, a measure of which is the appearance of the purpuric eruption. That the typical vibices can be associated with the presence of meningococci in the blood alone, apart from meningitis, is shown by Case II. (p. 63), in which petechiae and purpuric patches appeared while the blood culture yielded meningococci and the cerebro-spinal fluid was still clear and free from organisms or increase above the normal number of cells ; the cerebro-spinal fluid was not found infected until about 12 hours later. Further, many fulminating cases, if recognised early, not only yield positive blood cultures, but meningococci may be found in blood films taken from the ear or from a purpuric spot ; such films are well figured by A. C. Coles. These findings, in the presence of meningitis, do not of course necessarily prove that the meningococci were established in the blood stream prior to involvement of the meninges, as the organisms may possibly have escaped into the circulation from the pia-arachnoid space. Taken in conjunction, however, with cases in which meningococci are isolated from the blood stream prior to the appearance of meningitis (Case II.), together with those of meningococcal septicaemia without meningitis, both of which conditions may be accompanied by a purpuric eruption, the type of fulminating case mentioned above furnishes strong presumptive evidence that the infection of the blood is the primary factor, and is often of such overwhelming intensity as to cause death before the meningitis has time fully to develop. This termination is suggested by the post-mortem findings in a fair proportion of fulminating cases, the meninges appearing

as if involved only late in the disease, exhibiting congestion and a slight amount of turbid exudate about the optic chiasma and possibly on the under surface of the pons. In some cases, as in one reported by Thornley and Herringham and in another reported by Symmers, the only apparent signs of meningitis amount to a small collection of turbid fluid and a few flakes of pus in one or other of the ventricular cavities.

In some fulminating cases, however, autopsy reveals a more intense purulent meningitis, exudate not only appearing over the under surface of the cerebellum, pons and in the cisterna basalis, but also along the margins of practically all the vessels ascending up the sides of the cerebrum, as well as along the spinal cord.

Corresponding with the above-mentioned differences of degree in the meningitis found at autopsy, one may meet with at least two varieties of the fulminating type of case. This fact has not only been our experience, but may also be gathered from the recorded cases of others. The first variety, already described (Case XIV.), shows a well-marked purpuric eruption and succumbs to an intense blood infection, the meningitis being comparatively slight; the second variety, also terminating fatally within 12-48 hours of the onset, dies rather from an intense infection of the cerebro-spinal system. A purpuric rash may be present in these latter cases, but is more often absent; petechiae, however, are usually observed. The following case, dying within 14 hours of the onset of illness, is an example of this latter variety of the fulminating type:

CASE XV.—A man, aged 20, was suddenly taken ill during the evening; all day he had apparently been quite well. The first symptom complained of was headache, and a few hours later he vomited. In the morning, the patient was found delirious, the temperature being 99° F. and the pulse rate 120. On admission to hospital about 11 A.M., he was stuporose and exhibited a well-marked petechial rash but no purpuric spots. On reaching the ward the patient had a convulsive seizure, within half an hour of which he died. Lumbar puncture yielded a slightly turbid fluid showing, on microscopical examination, numerous polymorphonuclear cells and Gram-negative diplococci (intracellular and extracellular).

Post-mortem examination revealed considerable meningeal congestion and purulent exudate extending along the margins of almost all the cerebral vessels; over the under surface of the cerebellum and in the interpeduncular space the exudate was rather more abundant. It also extended along the spinal cord. On section of the brain the ventricles were found slightly distended with turbid fluid containing meningococci.

The differences observed in the two varieties of the fulminating type of cerebro-spinal fever may be explained as follows. They are, in reality, two extremes of the same species of intense infection by the meningococcus. In the ordinary case of cerebro-spinal fever, it is probable that the invading organism is merely carried by the blood to the meninges, constituting a temporary bacteriaemia rather than a true septicaemia (*vide* Chapter V.). In the first variety of fulminating case, there is an intense infection of the blood stream with definite multiplication of the organisms, leading to the appearance of a haemorrhagic eruption and the rapid collapse of the patient ; blood cultures at this stage will be positive. After a variable period, the organism settles in the meninges, but death may occur before the meningitis has time to become at all marked, owing to the patient having suffered too severely from the overwhelming intensity of the blood infection. Sophian states that he has noticed that if the purpuric fulminating cases can be tided over the first 24 or 36 hours, they run the course of the average case of cerebro-spinal fever. This was so in Case II. (p. 63) of our own series. Further, such fulminating types seen late in the course shortly before death, will usually fail to yield meningococci on blood culture ; this was so in some of our patients, the meningococci no doubt having left the blood stream. In the second variety of fulminating case, the septicaemic stage is shorter or may be absent, the blood stream merely acting as a vehicle for conveying the organism to its destination in the meninges. In the latter case, the infection of the central nervous system is sufficiently intense to cause death within 48 hours ; in such instances the purpuric rash is absent. Intermediate varieties, however, are met with ; thus, blood infection may occur and lead to the appearance of purpuric spots, but may be not sufficiently intense to kill the patient before the development of a considerable degree of meningitis. In one such case exhibiting a purpuric eruption, we obtained meningococci from a blood culture taken upon admission to hospital at 2 P.M. one afternoon. Lumbar puncture yielded a slightly turbid fluid under no marked pressure, yet showing meningococci in considerable numbers. The patient died at 10 A.M. on the following morning. Post-mortem examination showed well-marked generalised meningitis, purulent exudate extending along the margins of the cerebral blood-vessels from the base of the brain to the vertex. Sero-purulent exudate was also present over the pons and cerebellum ; there was no dilatation of, or pus in the ventricles.

Those cases proving fatal within 12 to 24 hours and showing well-marked purulent meningitis on post-mortem examination, are regarded by Netter as ambulatory cases with a terminal fulminating stage. The onset, however, in our experience is quite as sudden and abrupt as in the more usual (septicaemic) fulminating case, and no history suggesting an ambulatory stage is usually obtainable.

Regarding the haemorrhage into the medulla of the suprarenal glands, which is sometimes apparent in fulminating cases on post-mortem examination, Maclagan and Cooke draw attention to the fact that such haemorrhage would account for the diminishing, and later absent, blood pressure and muscular flaccidity invariably met with in the fulminating type of cerebro-spinal fever. They consider the hypotension directly due to the loss of epinephrin, the normal stimulus to the " myoneural function " of the sympathetic nervous system. To account for the muscular flaccidity in the same manner, one has to adopt the view that the suprarenals exert a tonic influence upon voluntary muscles as well as upon plain involuntary muscles. A diminishing blood pressure and muscular flaccidity, however, is almost invariably present towards death in all cases, irrespective of the clinical type, which terminate fatally, and becomes more marked as coma deepens. Further, we have not found haemorrhagic adrenalitis in all fulminating cases, although they have shown the clinical features common to the type. It must be admitted that destruction of the medulla of the suprarenal gland, theoretically, would tend to abolish blood pressure and produce collapse, but the primary factor is the general toxaemia.

Fulminating cases, and especially those in which a definite purpuric rash is absent, not infrequently remain undiagnosed during life. Lumbar puncture performed soon after death will sometimes enable a diagnosis to be made, but often autopsy alone reveals the true nature of the malady. Two cases, not seen by us during life, had remained unsuspected, no doubt owing to the absence of the usual signs of meningitis; in one case dying within 12 hours of the onset, lumbar puncture performed within half an hour of death gave the diagnosis of cerebro-spinal fever, which later was confirmed by autopsy. The second case, with a course of 36 hours, was diagnosed only on post-mortem examination; neither case showed a definite purpuric rash.

There is an important medico-legal aspect, as Netter has pointed out, in regard to fulminating cases of cerebro-spinal fever. The appearance of vomiting followed by coma, might well give rise to a

suspicion of poisoning. In one of the cases mentioned above as not being diagnosed during life, an abnormal reaction to anti-typhoid inoculation had been a suspected cause of death ; the patient received his second dose of vaccine (500 million organisms) at 11 A.M., the sudden onset of what proved to be cerebro-spinal fever occurring during the evening of the same day. Within 24 hours, the case terminated fatally, and autopsy revealed the true cause of death. A second patient who had fallen while on parade and later become comatose, was admitted to hospital as a possible case of fracture of the base of the skull. The true diagnosis was apparent on lumbar puncture.

Acute Fatal Type.—Fifteen cases of this type, upon which the following description is based, came under our observation at different times. The onset is almost invariably sudden and abrupt, consisting of an initial " chill," rapidly followed by severe headache and anorexia ; two patients only of our acute fatal cases had complained of a " sore throat," without other symptoms, for a few days prior to the sudden appearance of headache ; one other had just recovered from an attack of acute bronchitis. Following the initial chill, vomiting occurs within 6 to 12 hours ; this symptom is usually confined to the onset, but in a few cases it may persist until the end of the second day. Delirium next appears, usually within 24 hours of the onset of illness, but not infrequently within 6 to 12 hours. More rarely, coma may suddenly supervene without a preceding period of delirium ; one of our military cases, having complained of headache during the morning and taken no dinner, suddenly fell unconscious while waiting for a " roll-call."

Cases coming under observation on the second day of illness often exhibit violent delirium, occasionally bordering on mania, being extremely noisy, restless and kept in bed only with difficulty ; others are in a stuporose condition, taking no notice of questions or commands, but exhibiting hyperaesthesia and extreme irritability, strongly resenting any interference whatsoever. As a rule, the patient insists upon lying on his side, and resists any attempt to turn him into a supine position ; active withdrawal of the leg on plantar stimulation will often be found, together with well-marked rigidity of the cervical muscles and a positive Kernig's sign. Retention of urine is usually present ; apparent incontinence may be due to distension of the bladder with overflow.

The initial lumbar puncture will sometimes lead to temporary improvement, and the patient may be roused sufficiently to

answer questions, but in a comparatively short time he again relapses into delirium or stupor.

The stuporose stage is succeeded by coma, and patients first seen on the third day of the disease are frequently in this condition. Stupor or delirium, the latter low and muttering in type, with floccitation and carphology, may persist for a few days but coma eventually supervenes.

A petechial rash is almost invariably present by the second day ; in a few cases, a definitely purpuric eruption may be exhibited but it is seldom so profuse as in the fulminating type. Transient erythema is also observed, but a macular rash scarcely ever appears.

In all cases the initial temperature is high (101°-103° F.), and as a rule persists at about the same level with occasional remissions, until towards death on the 4th-7th day a rapid rise occurs. The temperature frequently reaches 106° or 107° immediately prior to death (Figs. 9 and 17).

During the second and third days the pulse is often comparatively slow (60-80) in proportion to the temperature ; in some cases it may vary from 100 to 120 per minute. In all, however, the pulse rate increases daily until, on the last day or two, it averages about 140. Some right-sided cardiac dilatation can frequently be made out, and in a few cases left-sided dilatation also.

The respirations during the first few days of illness are not markedly quickened (26-32) ; with the appearance of coma, they become more rapid and irregular, both in depth and rhythm, and Biot's type of breathing (p. 93) frequently develops. As the patient becomes more deeply comatose on the fourth or fifth day, mucus is heard rattling with each respiration, and a foetid discharge may occur from the nose and throat.

Herpes, in the majority of cases, does not appear ; in the few cases in which it is seen, it is merely labial in distribution. The urine usually contains a small amount of albumin (0·05 per cent Esbach).

The pupils are occasionally unequal and strabismus may be apparent on the second or third day ; nystagmus has also been observed. Muscular rigidity with well-marked stiffness of the neck, Kernig's and Brudzinski's signs, is a feature during the first four or five days ; head retraction is usually present in children, but in adults it is much less frequently seen. ·With the increase in depth of coma, however, general muscular flaccidity usually appears, and retention of urine is replaced by true paralytic incontinence.

The cerebro-spinal fluid is very turbid or purulent from the outset, and so remains throughout the course. At first, the intrathecal pressure is usually raised considerably, but this decreases towards the end ; the fluid, nevertheless, continues to flow quite freely and large amounts (60 c.c.) are usually obtained. On microscopical examination, abundant meningococci, as a rule, are seen, both intracellularly and extracellularly. Films made from the
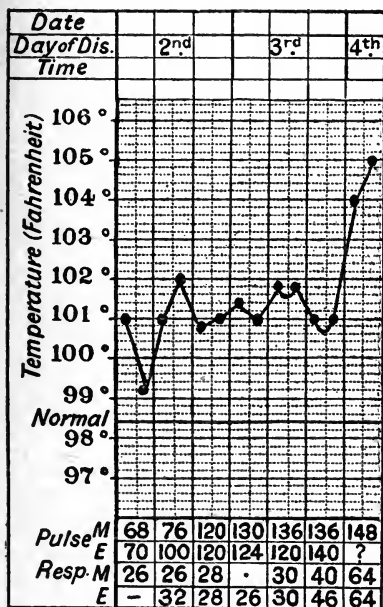
FIG. 16.—Acute Fatal Type.
Case XVI. Death on the fourth day of illness.
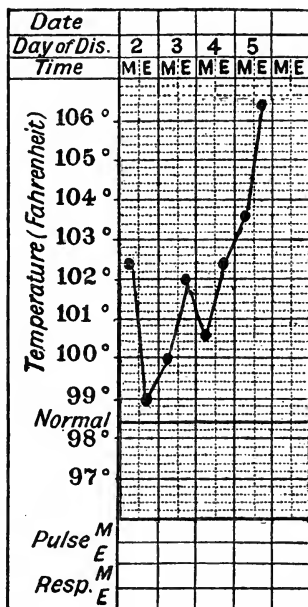
FIG. 17.—Acute Fatal Type.
Patient, aged 27, admitted on the 2nd day of illness and dying on the evening of the 5th day.

centrifugalised deposit of each of the daily specimens of cerebrospinal fluid, show little or no apparent change in the numbers of organisms present from the day of admission to hospital until the day of death ; in a few of our cases they were scanty or absent on the last day only.

Death, usually resulting from respiratory failure, occurs after a course lasting from 4 to 7 days.

The following case illustrates the acute fatal type :

CASE XVI. (Fig. 16). —*Acute Fatal Type.*— A corporal, aged 24, was admitted to hospital on the second day of illness in a

condition of profound stupor. According to a history obtained from men sharing the same billet, the patient had complained of dizziness about 11 A.M. on the previous morning; during the remainder of the day he seemed very poorly and was observed not to take any food. He refused to " report sick " but went to bed; about 11 P.M. he suddenly vomited, but afterwards appeared to " settle down." Early on the following morning he was found delirious and removed to hospital.

On admission to the isolation ward, the patient was stuporose and unable to appreciate any questions put to him, but strongly resented interference. In appearance he was pale, somewhat collapsed, and exhibited numerous petechiae on the limbs, together with a few purpuric spots; the latter were more numerous on and about the region of the hips. Retention of urine was present. The temperature was 102° F., pulse 68 and respirations 26. The pupils were slightly dilated and reacted sluggishly to light; a considerable degree of neck rigidity was apparent but no retraction. Kernig's and Brudzinski's signs were positive, the knee and ankle jerks very slight, and the plantar reflexes flexor with active withdrawal of the leg. The abdominal reflexes were absent, but the heart and lungs apparently normal. Lumbar puncture revealed a turbid fluid under considerable pressure, containing numerous meningococci, both intracellular and extracellular, and yielding a profuse growth of Type II. (Gordon) meningococcus. Thirty c.c. of anti-meningococcal serum were administered intrathecally.

Following the first lumbar puncture, the temperature fell to 99·2°, but the patient showed little or no improvement, being very restless and occasionally delirious during the remainder of the day. Fluids were swallowed fairly well. The urine contained a trace of albumin.

Third Day.—The patient became comatose during the early hours of the morning; at 10 A.M. the conjunctival reflex was just present, but he was quite unable to swallow; neck rigidity and Kernig's sign were still marked; the knee-jerks were very slight, but the ankle-jerks had disappeared. On plantar stimulation a feeble attempt was made to withdraw the leg. Sixty c.c. of turbid cerebro-spinal fluid were obtained, again showing numerous meningococci and giving a positive culture; the evening lumbar puncture yielded a similar result. Anti-meningococcal serum was given on each occasion.

Fourth Day.—The comatose condition had become more profound, all reflexes were absent and the previous neck rigidity was now replaced by flaccidity. Kernig's sign was absent, there being the merest slight rigidity of the hamstring muscles. The purulent cerebro-spinal fluid again showed abundant meningococci. The patient died at 2.15 P.M.

For results of autopsy in acute fatal tpye see p. 360.

Occasionally a terminal broncho-pneumonia may appear during the last day or two of illness, the respirations rising in rate to 50 or 60. Acute fibrino-purulent pericarditis may also occur, but as a rule is only discovered at autopsy. Owing to the comparatively

short duration of the course, other complications are infrequent, although in a few instances, chiefly children or adolescents, convulsive seizures may occur.

In a small proportion of cases, it appears that a meningococcal septicaemia may co-exist with the meningitis, being due either to an escape of organisms from the pia-arachnoid space or to a septicaemia persisting from the time of the initial invasion (*vide* p. 62).   One case, an adult, presenting a purpuric eruption, gave a positive blood culture on the third day, the organism being of the same type as that isolated from the cerebro-spinal fluid.   The patient died on the following day, and post-mortem examination revealed the well-marked cortical and basal meningitis usually seen in this type of case (*vide* Chapter XV. p. 360).

Beyond a temporary improvement, accompanied by a fall in temperature, following the initial lumbar puncture with or without serum administration, these cases show absolutely no response to treatment, even when cerebro-spinal fluid is evacuated every 12 hours.   Foster and Gaskell, in commenting upon the acute fatal type of cerebro-spinal fever, state that in their experience, owing to the difficulty in obtaining the patient earlier, lumbar puncture was rarely performed before the third day, when the symptoms were well advanced.   Had it been possible to puncture the patients earlier, they consider it fair to assume that alleviation, and in some cases cure, might have resulted.

We have received at least five cases of the acute fatal type on the second day of illness ; four were delirious or stuporose on admission to hospital, and one, though very drowsy, appeared quite conscious and rational on being roused.   The latter patient exhibited petechiae on the limbs and retention of urine, in addition to the usual signs of meningitis ; before evening he was delirious, and became stuporose next day.   In spite of energetic treatment these cases showed the same uniform downward progression towards death on the 4th-7th day as other cases of the same type but received later in the course, and in marked contrast to many other acute cases, apparently quite as severely ill on admission, who recovered after a short course.

The acute fatal type thus comprises a very distinctive group of cases of cerebro-spinal fever, the unsatisfactory issue of which is somewhat difficult to explain.   Foster and Gaskell point out that it appears as though this type represents " the power of endurance of the body in cases in which protective reactions were unable to

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develop." Consequently, these authors consider it reasonable to suppose that with an infection of such virulence, a period of about five days marks the longest time in which the primary onslaught of the disease is likely to prove fatal.

The post-mortem findings are characteristic, both cortical and basal meningitis being found (*vide* Chapter XV. p. 360). Occasionally, evidence of acute encephalitis may also be discovered, and more rarely cerebral haemorrhage.

Cases other than of the fulminating and acute fatal types may die within 4 to 7 days of the onset, and while the meningitis is improving, from an intercurrent broncho - pneumonia, or more rarely, from cerebral haemorrhage (*vide* p. 204).

Acute Cases which recover after a Short Course (8-14 days).—In the cases which we include in this group, the disease is of sudden onset, and the early clinical symptoms apparently quite as severe as those seen in the acute fatal type. In contrast to the latter, however, the condition of those patients recovering after a short course, rapidly, or in some cases gradually, improves from the outset, and the cerebro-spinal fluid is normal within 8 to 14 days of the onset. In a few cases, the disease, instead of exhibiting a gradual and steady improvement, remains more or less stationary during the first week, but rapidly improves during the second.

In all instances we encountered with the exception of two, the patients were received not later than the end of the second day of illness ; a few were admitted in a condition of irritable stupor within 24 hours of the onset. We consider that their comparatively rapid progress towards recovery is, at least, partly due to the fact that treatment was begun early, as well as to the nature of the treatment adopted, viz., the intrathecal administration of anti-meningococcal serum every 24 hours, in some cases every 12 hours, during the earlier part of the course and until the clinical improvement was definite and undeniable, followed by repeated daily lumbar puncture until a clear and normal cerebro-spinal fluid was obtained (*vide* Treatment, Chapter XVIII. p. 405).

The actual onset is almost invariably sudden and abrupt, with the usual severe headache and vomiting ; occasionally a cough or a " cold " may precede the initial symptoms. In all our cases delirium appeared within 24 to 36 hours, and in many it was rapidly succeeded by stupor, the patient nevertheless exhibiting extreme irritability and resenting interference. Other cases are violent, restless, and difficult to keep in bed. Retention of urine is often

present, less frequently true incontinence. Many cases show a greatly improved mental condition even on the day following the inception of treatment. In all, however, the stuporose or delirious state gradually disappears; nocturnal delirium persists in a few patients until between the fifth and tenth day in different cases, consciousness being normal in the day-time. With the improvement in the mental condition, normal sphincteric control is established, although transitory incontinence, owing to extreme precipitancy of micturition, may succeed retention of some days' standing. In a few cases received later than the second day of illness, definite coma may be present, yet the patient improves and recovery is established within 10 to 14 days.

Petechial rashes, showing the usual distribution, are frequently observed; a macular rash appears in some cases on the 2nd-4th day on the abdomen and limbs. Definite purpuric spots may even occur, but the lesions are few in number and never attain the size seen in cases of the fulminating type. Transient erythema is frequent.

The initial temperature is invariably raised and varies from 101° to 104° F.; in cases actively delirious, it is usually somewhat higher than in those stuporose. Following the initial lumbar puncture, practically all cases show a decided fall in temperature which, however, is succeeded by a subsequent rise to 101°-103° after an interval of 6 to 12 hours.

The general course of the pyrexia is, as a rule, irregularly remittent (between 99° and 103°), the evening temperature being the higher; occasionally the pyrexia is of a more continued type, while in a few cases it is more or less intermittent. In the majority of cases, the termination is by lysis, the temperature gradually falling towards the end of the course; the day on which it reaches the normal level is usually that on which a perfectly clear and normal cerebro-spinal fluid is obtained for the first time during the course of illness; occasionally the cerebro-spinal fluid is not found perfectly clear until a day or two after the temperature has reached normal.

In a certain proportion of cases the temperature falls by crisis, not infrequently almost immediately following the evacuation of the first clear cerebro-spinal fluid obtained. The crisis observed in these cases is to be regarded as a slight modification of a true crisis, such as is seen in pneumonia, etc. Although in a few cases of cerebro-spinal fever, delirium and incoherence occasionally disappear

with the sudden fall in temperature, there is never any sudden disappearance of neck rigidity and Kernig's sign ; these symptoms may sometimes appear slightly less marked after the pyrexial crisis, but nevertheless disappear gradually, many days elapsing before they are finally found absent. In a sense, this gradual disappearance of physical signs is comparable with the condition observed in lobar pneumonia, in which the pulmonary signs—bronchial breathing, impaired resonance, etc.—may persist for several days after the crisis has occurred, resolving only gradually. In cerebro-spinal fever, however, the spinal fluid gradually becomes less and less turbid, until immediately before the crisis, it shows the merest trace of opalescence, meningococci having disappeared some days previously.

During the pre-meningitic stage of the disease, which we have been able to observe in three cases of this type, the pulse is slightly quickened (100-110), but with the appearance of meningitis, it exhibits a fall to 60-80 ; in one case it was as low as 54 per minute. The general tendency is for the pulse rate to be slow during the first four or five days rather than later in the course ; cases in which, following the initial improvement, the condition remains stationary for the first week, not infrequently show a gradually rising pulse rate, which may reach 120 per minute ; when convalescence is established, however, it soon falls to normal. In those cases in which pyrexia terminates by crisis, the pulse rate, especially if it has reached a comparatively high level, at once drops *pari passu* with the fall in temperature. Other cases exhibiting a slow pulse rate (*e.g.* 60) throughout the course may show a slight rise (80) after the crisis.

During the course, with a few exceptions, the pulse rate shows little or no tendency to vary with the fluctuations of temperature ; in one case, indeed, the pulse was definitely slower when the temperature was raised and *vice versa*. A few cases exhibit a dicrotic pulse during the first week. The cases mentioned as developing a gradually increasing pulse rate up to 120 per minute, occasionally show some degree of cardiac dilatation, both right-sided and left-sided, the apex beat appearing outside the nipple line (*vide* Chapter VI., p. 91). In such cases, the blood pressure may show a tendency to fall and slight cyanosis is sometimes apparent.

During the early stage of illness, the respirations are slightly quickened, and they may also exhibit some variation in rhythm and depth ; at this stage, however, true Biot's respiration is not observed.

Herpes is of frequent occurrence in this type of case ; it appears from the 2nd to 5th day, but usually on the 4th. In distribution the eruption is, on the whole, less frequently confined to the labial region than in the acute fatal type, but shows a tendency to spread to the chin and even to the ears.

Albuminuria, varying from the merest trace of albumin to 0·05 per cent (Esbach), is somewhat common but seldom persists after the third or fourth day. In one of our cases yielding a clear cerebro-spinal fluid on the 10th day of illness, glucose was detected in the urine when the patient was admitted to hospital on the second day ; it was absent, however, on the day following and did not reappear.

Diplopia or strabismus may occur, but is usually only transient ; less frequently, definite paralysis of one or more of the ocular muscles can be demonstrated, but, as a rule, the paralysis is quite absent by the termination of the course of meningitis or disappears early in convalescence. In one case of our series, recovering after ten days, paralysis of both external recti was present from the 6th to the 10th day ; two weeks later, the functions of both muscles were normal. Another patient, aged 18 years, who recovered after 14 days, still exhibited complete paralysis of the left external rectus and marked weakness of the right six weeks after recovery.

Nystagmus may occasionally be met with ; it usually persists well into convalescence. Hyperaemia of the optic discs is occasionally found from the 3rd to 6th days, but definite optic neuritis is not frequent in these cases. Transient facial paralysis is sometimes observed.

The usual muscular rigidities with their dependent signs are usually well marked throughout the course of meningitis. Occasionally, head retraction is present by the fourth day, more especially in children and in spare subjects, and it may not have entirely disappeared by the time the cerebro-spinal fluid becomes clear and normal. As a rule, some degree of neck rigidity persists for a few days to a week after the cessation of pyrexia and the withdrawal of normal cerebro-spinal fluid ; Kernig's sign can frequently be obtained for some days after neck rigidity has disappeared.

The reflexes, both deep and superficial, are at first considerably diminished, the abdominal response frequently being absent ; the reflexes as a rule gradually increase as recovery approaches.

The first specimen of cerebro-spinal fluid withdrawn is either turbid or definitely purulent ; on microscopical examination, meningococci are usually numerous, both intracellularly and extra-

cellularly. The organisms, however, diminish in number and finally disappear as the fluid becomes less and less turbid. Finally, the cerebro-spinal fluid becomes quite clear to the naked eye, although a yellowish tinge may still be present when this stage is reached (*vide* Chapter X. p. 239).

As an example of the acute case recovering after a short course, the following instance may be cited :

CASE XVII. (Fig. 18).—The patient, aged 26, was admitted to
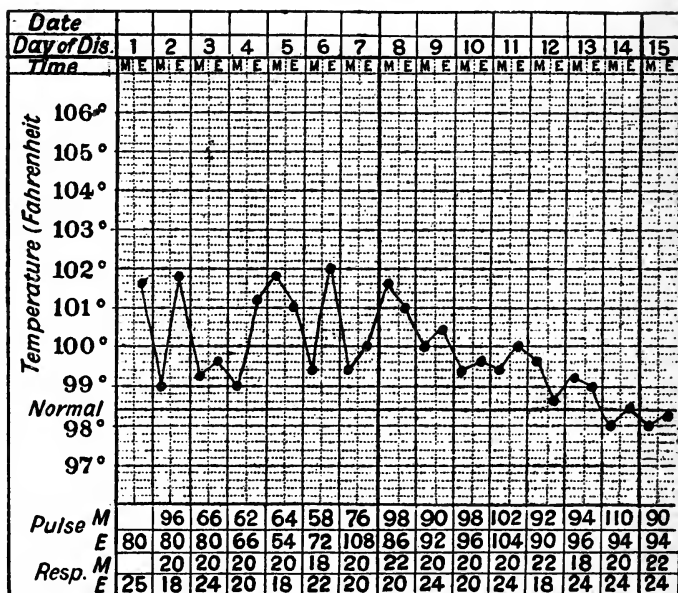
FIG. 18.—Acute case recovering after a short course.   (Case XVII. p. 150.)

hospital one morning in an extremely delirious condition, being noisy, restless and incoherent ; he was quite unable to appreciate questions put to him.   He had had a " cold " for about a week, and on the day prior to admission had shivered most of the afternoon and complained of severe headache during the evening.   Vomiting followed in the early hours of the morning, this symptom evidently being rapidly followed by delirium, in which condition the patient was found and sent to hospital.

On admission, the temperature was 101·6° F., pulse 80 and respirations 20.   In addition to delirium, incontinence of urine and slight photophobia were present.   Petechiae were apparent both on the limbs and on the trunk, and a scanty maculo-papular rash was present

on the extensor aspects of the limbs, backs of the hands and on the face. Neck rigidity, Kernig's sign and Brudzinski's sign were all present ; the tendon reflexes were slight and the abdominal reflexes almost absent. On attempting to elicit the plantar reflex the leg was actively withdrawn. On lumbar puncture, 40 c.c. of purulent fluid, under no greatly increased pressure, were obtained ; this, on examination, showed polymorphonuclear cells and numerous Gram-negative diplococci, chiefly extracellular. 30 c.c. of anti-meningococcal serum were administered intrathecally.

The patient was rather more conscious on the following day, but restlessness and delirium were again marked on the 4th and 5th days ; he then continued to exhibit periodic delirium, frequently trying to get out of bed, until about the 9th day, after which consciousness was normal. By the 8th day the sphincters had also become normal.

The cerebro-spinal fluid had ceased to be purulent by the 5th day ; with continued daily lumbar puncture, the fluid gradually became less and less turbid, until on the 14th day of illness it was quite clear and normal. No meningococci were seen on direct examination of stained films of the cerebro-spinal fluid after the 7th day, and no growth was obtained on culture after the first few days.

The temperature, pulse and respirations are shown in Fig. 18. Treatment consisted in lumbar puncture and serum administration once, sometimes twice, daily until the 8th day, lumbar puncture alone then being performed each day until a clear cerebro-spinal fluid was obtained (14th day) ; vaccine was also administered in the routine manner (*vide* p. 429).

Among the relatively common complications which occur in the type of case under discussion, the following may be mentioned ; arthropathies (*vide* p. 194), conjunctivitis, deafness and, usually almost at the end of the course, epididymitis (*vide* p. 194). Frequently the deafness improves as the patient progresses towards recovery, and during convalescence the hearing may almost fully return ; in other cases, however, the complication is persistent, and the patient remains completely deaf.

Acute Cases running a Long Course.—It is seldom that cases remain acute for longer than two weeks ; cases not recovering within this period and not exhibiting the characteristics of the progressively purulent type of the disease (*vide* p. 156), become subacute and eventually either recover or prove fatal owing to the development of hydrocephalus.

In a few instances, however, the patient remains acutely ill, with considerable pyrexia or even hyperpyrexia, for as long as four weeks, when the case usually terminates fatally. One such case is described on p. 84 (Case VI.) ; the patient continued acutely ill

for 31 days before death occurred. When admitted to hospital on the second day of illness, the case exhibited a purpuric rash, and purulent cerebro-spinal fluid containing numerous meningococci was obtained on lumbar puncture. During the course of illness hyperpyrexia was frequent (*vide* Fig. 10), and arthropathies also developed; meningococci were abundant in the cerebro-spinal fluid throughout the course. It is probable that such a case would prove more rapidly fatal, but coming under treatment early, lumbar puncture and serum administration defers, without completely preventing, the fatal issue.

Acute Cases becoming Subacute.—The onset and early part of the course in these cases is similar to those observed in either the acute fatal type or in acute cases recovering after a short course. Following the first few days, however, the patient, instead of becoming rapidly worse (acute fatal type), gradually improves; unlike the acute case recovering after a short course, towards the end of the second week, the patient fails to yield a clear cerebro-spinal fluid on lumbar puncture, but remains subacutely ill, which condition may continue for many days or even weeks. In a large number of cases, especially if lumbar puncture be continued, the patient eventually recovers after a variable interval; in other cases a chronic stage is reached, and the supervention of internal hydrocephalus may bring about a fatal result. Case XLVI. illustrates an acute case becoming subacute and subsequently being complicated by the occurrence of internal hydrocephalus, from which the patient recovered. Subacute types are dealt with later (p. 168).

Abortive Type.—This type is characterised by the fact that in spite of an acute onset, rigors, headache and vomiting, the symptoms subside almost as rapidly as they appeared, the patient being convalescent within three or four days. Neck rigidity and Kernig's sign are almost always present, and retention of urine is an occasional symptom, but a rash is very uncommonly observed. On lumbar puncture, the cerebro-spinal fluid is found under increased tension, but is often clear to the naked eye; when the deposit obtained by centrifugalising this fluid is examined microscopically, a few pus cells may be found and, occasionally, one or two pairs of diplococci; not infrequently no definite abnormality is revealed. A nasopharyngeal swab, however, invariably yields meningococci.

The following case illustrates the abortive type of the disease:

CASE XVIII. (Fig. 19).—The patient, aged 26 years, was admitted to a small local hospital with severe headache, vomiting, and in

a drowsy and delirious condition. The onset had occurred suddenly the evening before, with a complaint of shivering, headache, and, later, vomiting.

On admission to hospital the temperature was 102° F., pulse 60, and respirations 20. There was no rash, but neck rigidity and Kernig's sign were well marked. On lumbar puncture, a very slightly opalescent fluid was obtained ; it was under greatly increased tension, and showed meningococci both on direct microscopical examination and on culture. No serum was given.

On the following day, the patient's condition had greatly improved ;

FIG. 19.—Abortive Type.
(Case XVIII. p. 152.)
L.P., Lumbar puncture.

FIG. 20.—Aborted Case. (Case XIX. p. 154.)
The patient, aged 37, exhibited a rapid and effectual response to treatment.

his consciousness was quite normal, and headache was only slight. Two days later, neck rigidity and Kernig's sign were both absent, also, the temperature was normal and the patient stated that he felt quite well. Lumbar puncture (only the second performed) yielded a clear cerebro-spinal fluid, showing no more than the normal number of cells and no organisms.

An apparent abortive attack occurring in a carrier is described on p. 35 (Case I.).

A few cases of the abortive type, coming under observation soon after the onset of the disease, are more properly termed *aborted* cases, owing to the fact that they respond rapidly and effectually to

treatment. In such cases, the cerebro-spinal fluid is turbid, showing a polymorphonuclear leucocytosis and probably some diplococci, usually intracellular. The signs of meningitis are well marked. Following the intrathecal administration of anti-meningococcal serum, the pyrexia almost immediately declines, and next day the cerebro-spinal fluid is less turbid and the signs of meningitis less marked. Finally, on the third or fourth day, the temperature is definitely normal, the cerebro-spinal fluid clear, and all symptoms are absent.

The following case is an example :

CASE XIX. (Fig. 20).—A man, aged 37, was admitted to hospital early one morning in a condition of noisy delirium ; the onset had occurred suddenly on the previous afternoon and was accompanied by headache and vomiting. On admission, neck rigidity was moderate and Kernig's sign was well marked. The abdominal reflexes were absent and the plantars flexor ; on attempting to elicit the latter, the leg was actively withdrawn. No rash was apparent. The temperature was 101·4° F. and pulse rate 80. Lumbar puncture yielded a turbid fluid, showing numerous polymorphonuclear cells and a few intracellular diplococci. The patient was given 30 c.c. of anti-meningococcal serum.

On the following day, consciousness was normal and neck rigidity decidedly less ; the cerebro-spinal fluid was only slightly turbid, and no meningococci could be seen or cultivated. 30 c.c. of serum were again administered intrathecally. During this day the temperature did not rise above 99·2°.

Lumbar puncture next day yielded 25 c.c. of perfectly clear fluid, showing only an occasional polymorphonuclear cell ; beyond the merest limitation of complete flexion of the head and a Kernig's sign just positive, all symptoms were absent. Three days later, Kernig's sign also had disappeared.

In Case II. (p. 63), which exhibited a purpuric eruption prior to the appearance of signs of meningitis, the intramuscular injection of anti-meningococcal serum at this stage, together with the intrathecal administration of serum as soon as signs of meningitis were observed to be developing, appeared to bring about a similar rapid recovery.

M. Culpin has drawn attention to a peculiarity of pulse rate which occurs in cases of abortive cerebro-spinal fever. If careful records are taken, he states, the pulse rate will be found to drop at some time between the second and seventh day after the onset of the disease. The rate may fall to 60, or even 50, per minute, the period of slowing lasting from a few hours to a week. This observer

also states that if the patient is allowed up while the pulse rate is slow, he complains of a " swimming sensation in the head," and the pulse rate does not increase. Culpin states that the above sign was almost invariably present in those cases in which there existed clinical evidence supporting a diagnosis of abortive cerebro-spinal fever.

We have been able to confirm the above observations in a few abortive cases more recently met with; Figures 20 and 21 illustrate this slowing of the pulse rate in relation to the tempera-

Date																																					
Day of Dis.	2			3						4					5					6						7				8							
Time	1	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2	6	10	2
		PM		AM		PM		AM		PM		AM		PM		AM		PM		AM		PM		AM		PM		AM		PM		A

Temperature (Fahrenheit): 106° 105° 104° 103° 102° 101° 100° 99° Normal 98° 97°

| Pulse M | 80 | 80 | 76 | 84 | 60 | 70 | 64 | | 60 | 58 | 60 | 72 | 60 | 66 | 76 | 80 | 84 | 80 | 84 | 80 | 80 |
| Pulse E | | 76 | 76 | 82 | 60 | 72 | 60 | 64 | 60 | 60 | 74 | 68 | 60 | 76 | 82 | 84 | 84 | 84 | 86 | 82 | |
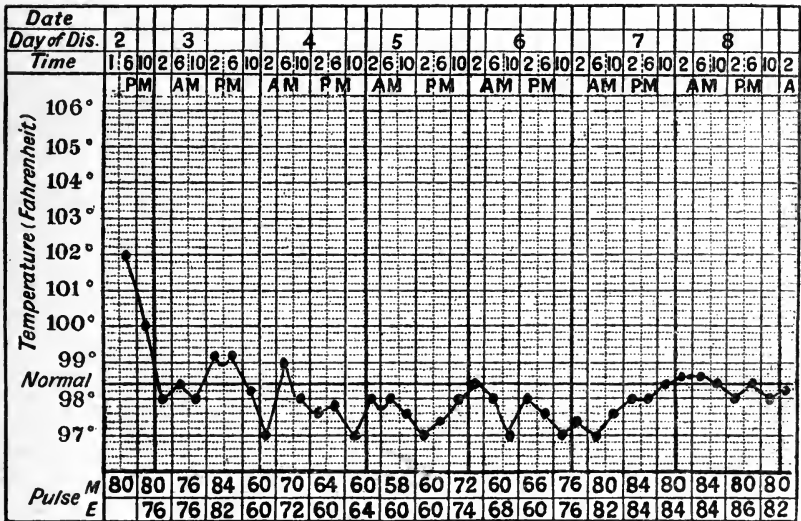
Fig. 21.—Abortive Type.

Four-hourly chart, illustrating the fall in pulse rate (4th to 6th day) following the cessation of pyrexia. It will also be seen that, at the same time, the temperature is subnormal.

ture. It may be added that we have also noticed, but by no means invariably, a comparative slowing of the pulse during the initial stages of convalescence in acute cases recovering after a short course. In the latter cases, as well as in those of the abortive type, following the disappearance of pyrexia, the temperature frequently remains subnormal for several days before reaching the normal level. In the majority of cases the pulse rate appears slowed merely in relation to the subnormal temperature, as in Figure 21, and when the temperature rises to normal the pulse also reaches its normal rate.

Cases occasionally occur in which an acute onset leads up to

only an abortive attack of the disease, the patient appearing quite well within 36 to 48 hours ; within three or four days, however, there occurs a second and more definite attack, which is considerably more severe and of longer duration. We have met with several such instances. These cases are really special forms of the recrudescent type of the disease, and will be found fully described under this heading (p. 162).

A " carrier " will sometimes complain of headache and pain in the neck and back ; the temperature may be 100° or 101° F., and the pulse rate 90 to 110, but vomiting is absent. No definite neck rigidity or Kernig's sign will be found, beyond the merest trace of rigidity of the hamstring muscles. On the following day the patient is much better or practically well. Such cases must not be mistaken for abortive types of cerebro-spinal fever. The condition no doubt is of " influenzal " origin.

SPECIAL TYPES

Progressively Purulent Type.—The characteristic clinical feature of this type of cerebro-spinal fever is a gradual and progressive increase in the purulent consistency of the fluid obtained on lumbar puncture ; this is associated with diffuse pus formation in the subarachnoid space and a corresponding increase in the severity of the symptoms, the cases invariably terminating in death. From the outset, the cerebro-spinal fluid, though occasionally turbid, is more frequently purulent, and at first, for a variable number of days, flows readily through the lumbar puncture needle. Gradually, however, the fluid increases progressively in density, becoming very thick and difficult to withdraw, until, during the last days of the course, only a few drops escape through the needle. Repeated lumbar puncture, even twice daily, serum administration and saline irrigation produce no change ; punctures performed in the higher interspaces (*e.g.* between the 11th and 12th thoracic vertebrae) yield the same purulent fluid in diminishing quantities. Occasionally, aspiration with a syringe will permit the withdrawal of a few additional drops of fluid, seldom more. Meningococci can usually be demonstrated in stained films of the deposit throughout the course ; sometimes on the last day or two the organisms may fail to grow on culture. In the majority of cases death occurs between the 8th and 15th days of illness.

The features observed clinically entirely coincide with the post-

mortem appearances (*vide* p. 361), the base of the brain being thickly coated with dense yellow pus. Smaller purulent deposits are occasionally seen on the cortex, but extensive involvement of this region is rare ; in a few cases, the ventricles are found to contain thick pus, but there is never present any excess of fluid.

Since some degree of suppuration occurs in practically all cases of meningitis, we have preferred the term " progressively purulent " to that of " suppurative," which designation is sometimes applied to the type of case under discussion.

Cases of the progressively purulent type are by no means infrequent. We have met with them only in adults ; the six cases on which the following description is based were between the ages of 19 and 29 years and constituted 24 per cent of fatal cases.

The onset is variable ; it may be either sudden and abrupt, consisting of the usual symptoms—headache, vomiting, etc.—or more gradual, the patient complaining of increasingly severe headache and intermittent vomiting for two or three days before finally coming under observation. Three of our cases had had a " cold " or " sore throat " for a week or two preceding the actual onset of cerebro-spinal fever ; in one, diarrhoea followed the initial vomiting. On admission to hospital, the case may be either acute or subacute, the latter in our experience being rather more frequent. Acute cases, admitted stuporose, may show a temporary improvement following the institution of treatment ; in all cases, however, the symptoms eventually become increasingly severe. Delirium, at first mild or merely nocturnal, becomes more pronounced towards the end of the first week, frequently culminating in great excitement or noisy restlessness, the patient continually trying to get out of bed. Wild delusions and visual hallucinations are often present ; for instance, one patient with an alcoholic history, saw bottles of beer and casks of whisky near his bed and asked for the former to be passed to him. Following the active delirium, a somewhat quieter period ensues, the patient lying listlessly in a state of muttering delirium, with occasional short intervals of clearer consciousness, but picking at the bed-clothes or passing his hands above his face as if trying to catch imaginary objects (floccitation and carphology). Death sometimes occurs during rambling or muttering delirium without the supervention of coma.

Petechiae may be present in an acute case, eventually becoming progressively purulent, or a macular rash may appear within the first five days ; frequently, however, no rash is observed.

The temperature, at first, is moderately high (100°-102° F.), and shows the usual fall after the initial lumbar puncture. As a general rule, the course of pyrexia is irregularly remittent, the higher figure (102°, seldom reaching above 103°) being recorded in the evening; more rarely, the pyrexia may be somewhat intermittent in type. Although a rise in temperature to 102° F. may precede death, the extreme figure so often recorded in the acute fatal type is not commonly met with; quite often the temperature falls or remains unaltered towards death.

The pulse rate shows a gradually increasing rise from 74-80 to 120-140 as the termination of the course approaches.

Herpes is infrequent; it was observed in one case only, and was then entirely labial in distribution.

Retention of urine, which may not appear until the sixth or eighth day, is a marked feature in most cases. Acute cases on admission to hospital, may show retention or incontinence, but with temporary improvement, normal control is frequently regained for a period of four or five days, following which retention accompanied by increased delirium supervenes. In two cases, the appearance of retention at the beginning of the second week of illness was accompanied by persistent hiccough. Once established, the retention usually persists until the end of the course, although in a few cases it may be replaced by incontinence shortly before death.

The pupils are somewhat dilated and sluggish in their reaction to light; strabismus frequently occurs late in the course, and occasionally the optic discs may show some hyperaemia.

Neck rigidity and Kernig's sign are constant features throughout the illness, and head retraction is more frequent than in adults of the acute fatal type.

The abdominal reflexes are either absent throughout or disappear very early in the course. In one case only, on the fourth day, was an extensor plantar reflex obtained; it was then merely unilateral.

In addition to floccitation and carphology, other motor disturbances may be present. Spasmodic twitchings of the limbs or head are frequently observed during the last few days; in one case, an epileptiform convulsion seizure occurred on the ninth day of illness, followed by coma and death within a few hours.

A terminal bronchitis or broncho-pneumonia is not infrequent in these cases.

The following case illustrates the progressively purulent type of the disease :

CASE XX. (Fig. 22).—A soldier, aged 28, having had a sleepless night, complained of headache in the morning ; during the course of the day, he had one or two shivering attacks, and in the evening was sent into hospital with a temperature of 102° F. as a case of influenza.

On admission, he was stated to complain of headache and soreness in the throat ; his mental condition was normal. During the night, however, he became very restless, and vomited about 3 A.M. ; when seen by one of us at 7 A.M., he was in a condition of irritable stupor, lying on his side with all limbs flexed, flushed, stertorous and resentful of interference. The temperature was 102° F., pulse 80 and respirations 20. Neck rigidity and Kernig's sign were both present ; the abdominal reflexes were absent and the plantars flexor. On stimulation of the sole of the foot, however, the leg was at once actively withdrawn. Retention of urine was present. Lumbar puncture yielded 40 c.c. of purulent fluid containing numerous meningococci. 30 c.c. of anti-meningococcal serum were administered intrathecally.

During the evening and following morning, the patient showed alternate periods of more or less normal consciousness and rambling delirium ; until the end of the 6th day he remained in practically the same condition. At times he would give his name and age correctly, but at others exhibit delusions, e.g. that his wife was sitting beside him, that he was

FIG. 22.—Progressively Purulent Type.
(Case XX. p. 159.)

in prison for a crime he had committed, etc. From the 7th to 9th days a continual low muttering delirium was present, with floccitation and carphology. On the 10th day the patient was still delirious with occasional shouting. The respirations were very shallow, and the left external rectus muscle was paralysed. Death occurred at 4 P.M.

Retention of urine, together with slight albuminuria, persisted throughout the illness ; Kernig's sign and neck rigidity were invariably present, and at no time was the abdominal reflex obtainable.

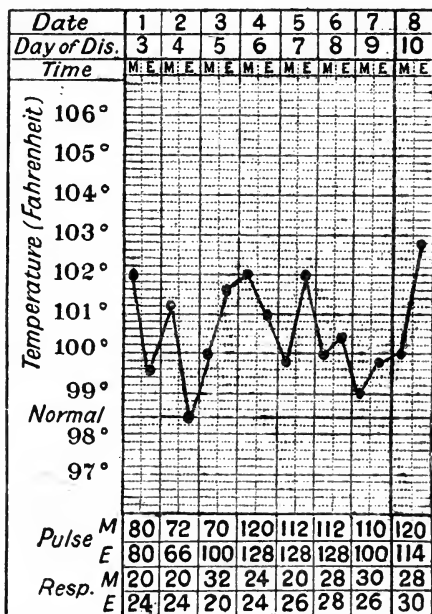The lumbar punctures and condition of the cerebro-spinal fluid are detailed in the following table :

Day of illness.	Lumbar puncture.	Amount withdrawn.	Appearance.	Therapeutic Serum.	Microscopical Examination.	Culture.
3rd	Usual site	40 c.c.	Purulent	30 c.c.	Polymorpho. cells with numerous meningo-cocci intra-cellular and extra-cellular.	+ Type II.
4th	,,	35 c.c.	,,	30 c.c.	,,	,,
5th	,,	15 c.c.	Thick yel-low, spon-taneously coagulable.	No serum would flow in.	,,	,,
6th	No fluid ob-tainable be-low 1st lum-bar verte-bra; fluid obtained from be-tween 1st lumbar and 2nd thoracic.	10 c.c.	,,	5 c.c.	Ditto, but organisms chiefly in-tracellular.	,,
7th	Fluid aspir-ated from between 1st and 2nd lumbar.	8 c.c.	,,	No serum would flow in.	,,	,,
8th	Three inter-spaces en-tered, up to that be-tween 11th and 12th thoracic.	No fluid obtain-able.	...	...	...	...
9th	Fluid ob-tained from between 1st and 2nd lumbar, nil below.	2 c.c.	Densely purulent.	No serum would flow in.	Polymorpho. cells and a few lym-phocytes, meningo-cocci chief-ly intra-cellular.	+ Type II.
10th	Fluid from between 11th and 12th thor-acic, no fluid ob-tainable below this level.	A few drops only.	,,	,,	Numerous polymorph. cells; no organisms seen.	No growth.

Autopsy.—Thick massive accumulation of pus over the base of the brain, completely obliterating the under surface of the pons and medulla, and extending laterally to the adjacent part of the cerebellum. The dense pus extended forwards to the posterior edge of the optic chiasma and also down the spinal cord in large amounts. There were one or two small purulent foci in the meninges in the neighbourhood of the great longitudinal fissure on each side of the cerebrum, but beyond these no pus was visible on the upper or lateral aspects of the brain.

Four of the cases proving to be of a progressively purulent type did not come under our observation until the third or fourth day of illness. Two, at first subacute, had been regarded elsewhere as cases of influenza, until the appearance of delirium demanded more careful investigation. It might be considered that if treatment by lumbar puncture and the intrathecal administration of serum had been possible earlier, the subsequent course would have been considerably modified. The remaining two cases, however, came under treatment on the second day of illness, but died on the eighth and tenth day respectively after typically progressively purulent courses ; repeated lumbar puncture and serum administration appeared without effect on the downward progress.

A feature of interest was that five of the six cases of the progressively purulent type had pre-existing pulmonary or renal disease, and gave evidence on post-mortem examination of permanent changes in the kidneys or lungs, thus :

(1) Aged 29.—Was alcoholic and had had pneumonia five years previously. Post-mortem, old and firm pleural adhesions of both lungs were found.

(2) Aged 26.—History of severe " winter cough." Post-mortem, the left lung was adherent posteriorly and to the diaphragm. Fibro-caseous tuberculous nodules, about the size of a pea, were present at the apex of the right lung and at the lower edge of the upper lobe of the left lung.

(3) Aged 28.—Previous history of pneumonia. Firm pleural adhesions of left lung posteriorly and laterally ; upper lobe of right lung firmly adherent to the parietal pleura. Old tuberculous cicatrices at right apex.

(4) Aged 24.—Complaint of " weak heart " for two years prior to his fatal illness. Clinical and post-mortem evidence of early chronic nephritis.

(5) Aged 28.—Clinical evidence of chronic nephritis. No autopsy.

Recrudescent Type.—In this type of the disease, the progress does not exhibit a uniform advance but, following a decline, which

11

may last several days, both the pyrexia and symptoms of meningitis reappear with their previous intensity. The course may thus be interrupted by one or more such " crises." The apyrexial periods are seldom of longer duration than five or six days, although Sophian records a case which continued without rise of temperature for ten days. The remissions of pyrexia occasionally occur with such regularity that some authors have compared the course with that of tertian malaria ; in rare instances, every third day the temperature has reached 104° F., falling to normal after 24 hours. As a rule, however, the pyrexial periods are of longer duration and do not recur with such definite regularity.

The explanation of recrudescent cases lies in the fact that during the intervals of remission, the meningitis is merely quiescent, and after a short period recurs with renewed activity. Not infrequently, meningococci disappear during the apyrexial periods, and no organisms can be seen or cultivated from the cerebro-spinal fluid ; their return, however, usually coincides with the reappearance of a raised temperature and increased symptoms of meningitis.

A certain degree of neck rigidity is usually present throughout the period of decline, and Kernig's sign almost invariably persists ; these signs serve to differentiate a recrudescence from a true relapse (*vide* Relapses, p. 174).

The onset of the disease differs in no way from that of other types; herpes is common and complications are equally liable to occur. In our experience, especially if lumbar puncture be repeated daily and anti-meningococcal serum administered intrathecally during the acute exacerbations, the cases usually terminate in recovery. When death occurs, it is generally owing to the development of hydrocephalus.

In some instances, a primary acute onset may lead merely to an abortive attack of the disease, the patient appearing quite well after 36 or 48 hours. A few days later, however, a more definite attack ensues, which is usually of considerably longer duration. We have met with several such instances, of which the following case is an example :

Case XXI. (Fig. 23).—The patient went to bed one night feeling quite well, but in the early hours of the morning awakened with severe headache, great thirst, and a sore feeling in the throat ; a short time later he vomited. In the morning, feeling faint and dizzy, he " reported sick " and was sent to the local hospital. On arrival there, his temperature was 102·8° F., pulse 86, and some " spots " were said to

be present on his arms and legs. Towards evening, the temperature fell
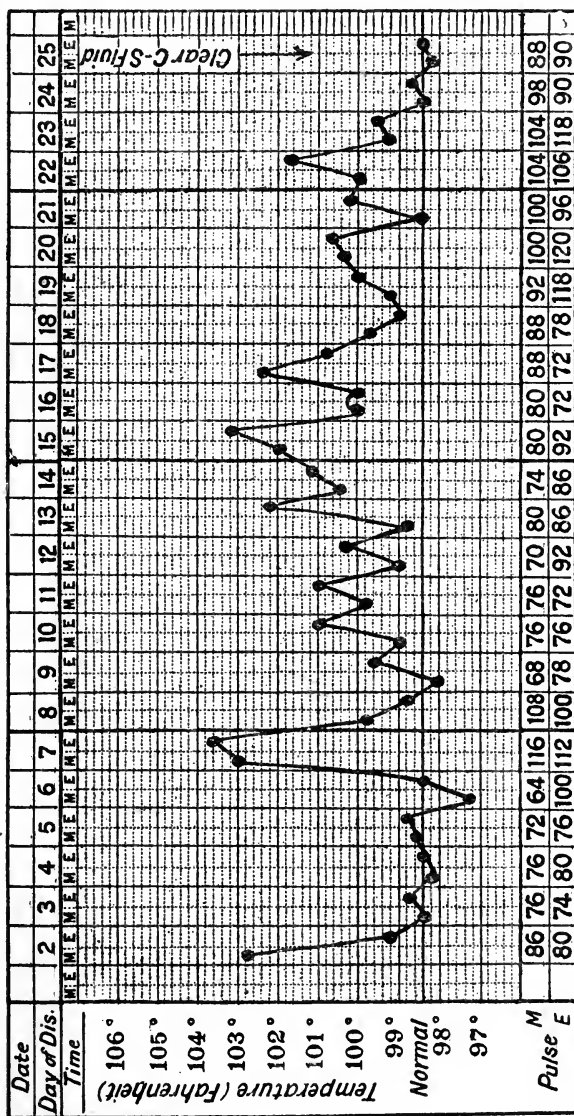to normal, and next day he felt considerably better, complaining only

FIG. 23.—Recrudescent Type. (Case XXI, p. 162.)
Showing an initial abortive attack.

of a slightly sore throat. On the following day, the temperature was
normal and he appeared quite well.

Thus he continued until the afternoon of the fourth day following
the decline of the initial pyrexia, when suddenly he had several rigors

in rapid succession, the temperature falling to 97·2° ; soon afterwards, violent headache appeared. During the night he vomited twice, the temperature rising to 103° and the patient becoming delirious.

On the following day, the case came under our observation, the patient being drowsy, incoherent and delirious ; incontinence of urine and faeces was also present. The temperature was 100° F. and pulse 88 ; cervical rigidity was well marked, together with some slight head retraction, and Kernig's sign was positive. Lumbar puncture yielded 60 c.c. of purulent cerebro-spinal fluid under increased pressure and containing numerous meningococci. The patient was slightly more conscious next day ; incontinence had ceased by the fourth day of the recrudescence, and by the fifth his mental condition was practically normal. The course continued for 18 days following the recrudescence of symptoms (total course 24 days), meningococci being present in the cerebro-spinal fluid until the 13th day. Extreme head retraction was a marked feature throughout the course, and persisted, in the absence of all other symptoms, long after the decline of pyrexia (vide p. 110) and the withdrawal of clear cerebro-spinal fluid.

The treatment in this case consisted of serum administered intrathecally (in 30 c.c. doses) on each of the first eleven days of observation ; lumbar puncture was then continued for seven further days, until the cerebro-spinal fluid was quite normal (24th day of total illness). Polyvalent vaccine was given at intervals of four days in doses increasing from 250 millions to 2000 millions.

The more usual variety of recrudescent case exhibits a course continuing for several weeks or even months, and interrupted by the reappearance of pyrexia and meningeal symptoms following an interval of apparent improvement. In one of our cases, a bugler aged 15, the total course continued for over two and a half months (about 80 days) ; after a more or less continued pyrexia for the first twelve days, nine of such " crises " occurred at irregular intervals, each lasting from one to four days. During those apyrexial periods occurring after the second week, meningococci were not usually seen or cultivated from the cerebro-spinal fluid, and neck rigidity was frequently almost absent, Kernig's sign being much diminished ; meningococci, however, reappeared when the temperature rose. Vomiting, incontinence and increased muscular rigidity also recurred with the recrudescences. Progressive emaciation was a marked feature, and after the 51st day, hemiplegia began to develop, a recrudescence having occurred on the 49th day. The following description deals with the leading features of the case, and serves to illustrate the type:

CASE XXII. (Fig. 24). — The onset had occurred somewhat

gradually, the patient complaining of feeling chilly one afternoon, and some hours later experiencing headache and abdominal pain.   Vomiting
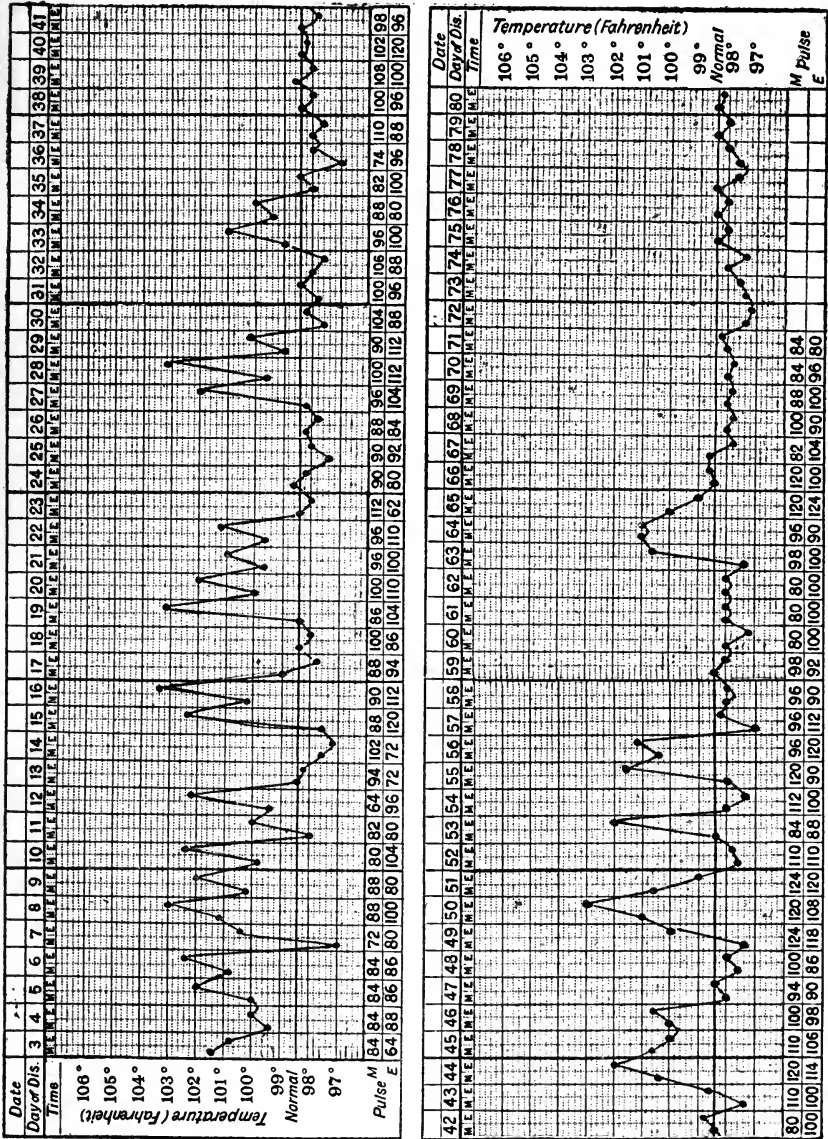

FIG. 24.—Recrudescent Type.   (Case XXII, p. 164.)

did not appear until the following evening.   He was sent to hospital next day.

On admission, the temperature was 101·4° F., pulse 94 and respirations 22. Neck rigidity was moderate, Kernig's sign present but unequal on the two sides, and herpes was commencing on the margin of the upper lip. A fading macular rash was noticed on the legs and feet. On lumbar puncture, 45 c.c. of slightly turbid fluid were obtained ; no organisms were seen on direct examination of stained films of the centrifugalised deposit, but in culture a growth of Type II. (Gordon) meningococcus appeared.

During the first 12 days of illness, the temperature continued irregularly, finally falling to normal on the 13th day. The following table summarises the subsequent recrudescences, together with the accompanying symptoms and signs :

Temperature reached normal on 13th day of illness.

14*th Day.*—Neck rigidity practically absent and Kernig's sign more marked on the right side than on the left. No meningococci seen in the cerebro-spinal fluid.

(1) 15*th*-16*th Day* (36 *Hours*).—Increased neck rigidity ; Kernig's sign positive. No organisms seen, but obtained in culture. No meningococci were seen in or cultivated from the cerebro-spinal fluid during the apyrexial interval.

(2) 19*th*-22*nd Day* (4 *Days*).—Vomiting, increased muscular rigidity ; meningococci reappeared both on direct examination and in culture. From the 23rd day, neck rigidity disappeared and Kernig's sign was much reduced but did not disappear.

(3) 27*th*-29*th Day* (2½ *Days*).—Vomiting, increased muscular rigidity and incontinence.

(4) 33*rd and* 34*th Days* (36 *Hours*).—Vomiting, stupor and incontinence. Food refused and nasal feeding performed. Meningococci reappeared in cerebro-spinal fluid on direct microscopical examination, but not in culture. During the apyrexial interval, cervical rigidity disappeared, mental condition became normal, Kernig's sign diminished, and no meningococci could be seen in or cultivated from the cerebro-spinal fluid.

(5) 44*th*-46*th Days* (3 *Days*).—Vomiting and increased muscular rigidity. Meningococci on direct examination.

(6) 49*th*-51*st Day* (2½ *Days*).—On the 49th day vomiting occurred. No meningococci could be detected in the slightly turbid cerebro-spinal fluid, but a good growth was obtained in culture. Polyuria was present. On the 51st day hemiplegia began to develop. Apyrexia for 36 hours.

(7) 53*rd Day.*—Evening temperature rose to 102° F. without any definite increase in symptoms. Apyrexia for 36 hours.

(8) 55*th and* 56*th Days* (36 *Hours*).—Vomiting, incontinence and increased neck rigidity. During the apyrexial interval, cervical rigidity disappeared, but not Kernig's sign.

(9) 63*rd*-65*th Day* (3 *Days*).—Very slight increase in neck rigidity. No vomiting, but symptoms of collapse. Meningococci were seen on

direct examination of the cerebro-spinal fluid, but were not obtained in culture.

Following this last recrudescence, the patient gradually improved. No further recrudescences occurred, and by the 80th day the cerebro-spinal fluid was quite clear and all symptoms excepting the residual hemiplegia (*vide* Complications, p. 197) were absent.

It will be seen that in the above case, during the apyrexial periods, meningococci were frequently not found either on direct examination or on culture of the cerebro-spinal fluid, while when the recrudescences occurred, the organisms reappeared either on direct examination or in culture. Further, although neck rigidity was often absent between the crises, Kernig's sign persisted throughout. This fact is important as it serves to distinguish a recrudescence from a true relapse (*vide* p. 174).

The above case occurred early in 1916 before we adopted the method of repeating lumbar puncture daily until a clear and normal cerebro-spinal fluid is withdrawn. Consequently, although the patient was punctured daily and received serum intrathecally for the first eleven days of the course, that is, until he had definitely improved, subsequently, the operation was repeated only when the recrudescences occurred. Since adopting repeated daily punctures until the cerebro-spinal fluid is clear and the temperature normal, we have met with no similar type of case. Recrudescent cases have occasionally occurred, but the course has been limited to one recrudescence only, and as a rule this has speedily yielded to a renewal of serum treatment. Such a case is illustrated by Figure 25 ; the patient was admitted on the fourth day of illness, and by the tenth day the temperature reached normal : no meningococci were found after the fifth day. Serum was given for the first four days of observation (4th to 7th inclusive), followed by daily lumbar puncture ; the cerebro-spinal fluid remained very slightly turbid. On the 15th day a recrudescence occurred, being characterised by increased Kernig's sign and a return of pyrexia ; meningococci were not seen in films of the cerebro-spinal fluid, but appeared in culture. Serum administration was resumed for four further days (15th to 18th inclusive), lumbar puncture being continued daily until the 22nd day, when the cerebro-spinal fluid was quite clear and the temperature normal.

Recrudescences may occur a considerable time, often months, after apparent recovery has taken place, and thus may easily be mistaken for a true relapse (*vide* Relapse, p. 174). In the interval,

however, the patient has never been really well, and if examined, Kernig's sign will have been found to persist. Such delayed recrudescences may lead to hydrocephalus resulting in death (*vide* p. 217).

In a few cases, an intercurrent pneumonia, developing while the meningeal symptoms are improving, will apparently permit a recrudescence of meningitis, owing, no doubt, to a further lowering of general resistance. This occurred in Case XXX. (p. 188), the
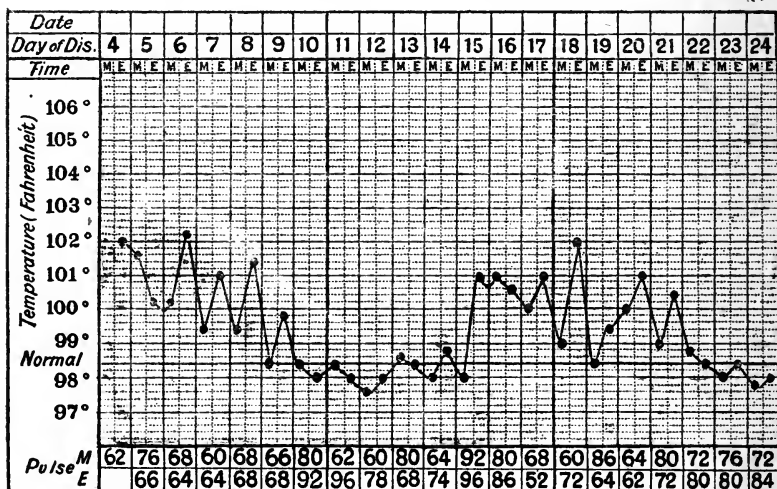

FIG. 25.—Recrudescent Type.

Temperature reaching normal on 10th day of illness, a recrudescence occurring on the 15th day and terminating in recovery. (See text, p. 167.)

patient dying on the 16th day of illness, when the pneumonia had practically disappeared.

SUBACUTE TYPES

Mild Subacute Cases.—In this type the course seldom lasts for longer than 6 to 9 days. The cases are not infrequently met with towards the decline of an epidemic, and in adults are often sporadic. The onset is sometimes preceded by a period of malaise, such as a " cold " or " sore throat." Occasionally the onset is gradual, consisting of gradually increasing headache and general pain, until the patient is compelled to remain in bed. Vomiting is often absent.

The mental condition usually remains normal throughout the

course of illness, especially if the patient comes under treatment soon after the onset. In a few cases, delirium occurs during the early stages; in others it is merely nocturnal. The sphincters are not usually affected. The initial temperature varies from 100° to 103° F. but shows a gradual and steady fall, with a few morning remissions, until it reaches its normal level; by this time the cerebro-spinal fluid is quite clear. Some degree of neck rigidity and Kernig's sign is invariably present, and herpes may develop. Lumbar puncture yields a slightly turbid fluid containing relatively few meningococci; these, however, rapidly disappear as the patient improves.

The following case illustrates this type:

CASE XXIII. (Fig. 26). —Three days before admission, this patient, aged 30, had left an isolation hospital convalescent from an attack of rubella. During the early morning of the day preceding his admission to hospital, he had complained of headache, the pain preventing his sleeping; during the course of the day the headache gradually became more intense, and on the following day, he " reported sick." No vomiting occurred.

On admission to hos-

Date									
Day of Dis.	2	3	4	5	6	7	8	9	10
Time	M E	M E	M E	M E	M E	M E	M E	M E	M E
Pulse M	92	86	72	64	80	60	76	76	78
Pulse E	88	80	60	68	56	60	64	70	80

FIG. 26.—Subacute Case—mild.
(Case XXIII. p. 169.)

pital, the temperature was 102° F. and pulse 92; neck rigidity and Kernig's sign were both moderate. His consciousness was quite clear and the sphincters unaffected. On lumbar puncture, 50 c.c. of turbid cerebro-spinal fluid were withdrawn and showed the presence of intracellular meningococci.

Following the initial lumbar puncture and serum administration the patient rapidly improved, no meningococci being seen in the cerebro-spinal fluid after the third day; by the seventh day, the cerebro-spinal fluid was clear to the naked eye, the temperature normal, and the patient quite free from subjective symptoms. Herpes appeared on the fourth day, neck rigidity was absent by the eighth day, and Kernig's sign disappeared five days later.
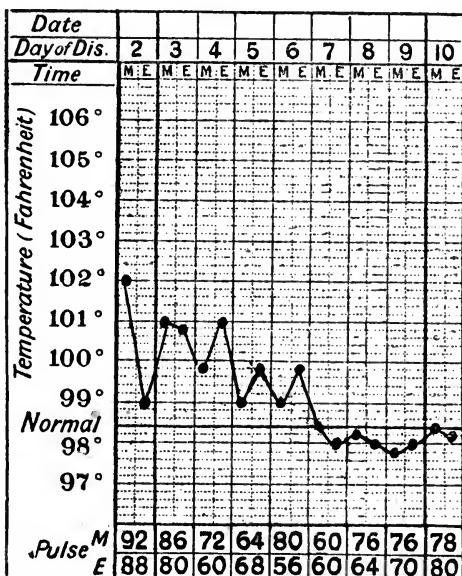
The patient was treated with anti-meningococcal serum administered intrathecally in 30 c.c. doses on each of the first four days in hospital ; lumbar puncture was then repeated daily until the seventh day of illness.   Three doses of polyvalent vaccine were also given at the usual intervals.

Moderately Severe Subacute Cases.—The duration of the course in these cases varies from 10 to 18 days, and usually terminates in recovery.

The onset may be sudden or gradual ; in the latter case, the patient complains of increasingly severe headache and pain in the back and limbs, which, as a rule, culminates in vomiting.   In a few cases, a " cold," cough or " sore throat " precedes the actual onset.

Extreme drowsiness or delirium is often present in the early stages of meningitis; although drowsy and confused, the patient may, when roused, answer questions intelligibly.   Delirium may occur at irregular intervals for the first five or six days, following which consciousness becomes normal.   Retention of urine is sometimes present at the onset of meningitis, but normal control is usually soon regained.   Kernig's sign and neck rigidity are well marked, and by the fourth day, head retraction may appear, especially in children and young adults.   In the majority of cases, the pyrexia is irregularly remittent (99°-103° F.), and shows a tendency gradually to fall towards the end of the course ; in some cases the pyrexia may be intermittent.   The pulse rate remains relatively slow throughout the illness, and seldom reaches above 90 per minute.   Herpes is frequent and rather more common than in acute cases.   Strabismus and a degree of optic neuritis may be observed.   We have also seen this type of case complicated by arthropathies and lobar pneumonia.

Lumbar puncture yields a turbid fluid in which meningococci are easily found ; the fluid gradually becomes less and less turbid until, by the time the temperature reaches normal, it is clear to the naked eye and free from polymorphonuclear cells and organisms.

The following case is an example of this type :

CASE XXIV. (Fig. 27).—The patient, aged 26, was admitted to hospital on the third day of illness.   He had had a " cold " for about two weeks, but two days prior to admission had experienced sudden and severe headache ; he remained in bed that day but could not sleep ; later vomiting occurred.

On admission to hospital he was extremely drowsy and exhibited occasional periods of delirium ; at times, he could be roused sufficiently to answer questions.   Retention of urine was also present.   Cervical

rigidity, Kernig's sign and Brudzinski's signs were all well marked. The temperature was 101·8° F. and the pulse 72. On lumbar puncture, 40 c.c. of turbid fluid were obtained ; this on microscopical examination showed very degenerate pus cells and a few Gram-negative diplococci, both intracellular and extracellular. Culture yielded a Type II. (Gordon) meningococcus.

Retention of urine had disappeared by the second day in hospital (4th day of disease), but occasional delirium persisted for a few days longer. Labial herpes appeared on the 5th day, the lesions eventually
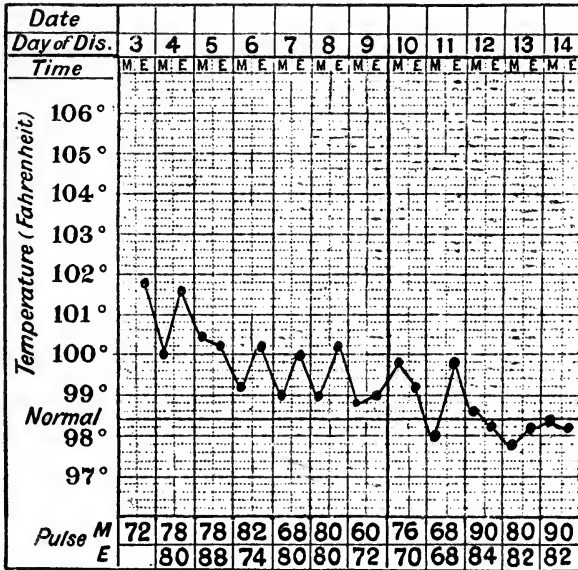

Fig. 27.—Subacute Case—moderately severe.
(Case XXIV. p. 170.)

spreading to the chin and nose. Transient paresis of the left external rectus muscle was present from the 5th to 9th days.

No organisms were found in the cerebro-spinal fluid after the 6th day, and by the 12th day, when the temperature reached normal, the fluid was quite clear. Treatment was carried out by the intrathecal administration of serum and repeated daily lumbar puncture according to our usual method.

Subacute cases, both mild and moderate, frequently do not come under special observation until some days have elapsed since the onset of the disease. Consciousness often being normal, they are frequently regarded as cases of influenza, and the true nature of the

disease not suspected until the persistence of pyrexia or the appearance of delirium demands a more searching examination. In such instances, the delay of therapeutic measures—lumbar puncture and serum administration — naturally tends to prolong the course. Occasionally we have not received subacute cases until from the 10th to the 14th day of illness, and although usually terminating in recovery, they have been inclined to run a chronic course (*vide* p. 435).

CHRONIC TYPES

Ordinary Chronic Type.—Cases originally acute or subacute may eventually become chronic. During the second or third week, some cases originally acute gradually merge into a subacute and finally a chronic stage. Other cases may exhibit a special form of chronic course, recrudescent (Case XXII. p. 164), which has already been described.

In cases terminating fatally after three or four weeks of illness, death is almost invariably due to hydrocephalus, either internal or generalised. Consequently, chronic cases not only resemble each other in their clinical features but also in their pathological anatomy. They are characterised by the protracted and lingering course, slow but steady deterioration, and the symptoms of gradually increasing intracranial pressure. The temperature may vary considerably but is often normal or subnormal. Rigidity of the neck and Kernig's sign persist throughout. Incontinence of urine and faeces is usually a marked feature, and the patient becomes very tremulous. Emaciation progresses at a rapid rate in spite of the ingestion of large quantities of food. Sooner or later the symptoms indicative of hydrocephalus appear, and the description of the course coincides with that of this serious complication (*vide* Chapter IX.).

The duration of the course of chronic meningitis may be from six weeks to six months or even longer. Aaser records one chronic case, in a child, in which meningococci were found in the cerebro-spinal fluid two and a half years after the original attack (*vide* p. 216).

The chronic form of cerebro-spinal meningitis was the classical type formerly described in text-books. Since the introduction of specific serum therapy, however, it is relatively uncommon and usually occurs only in untreated cases or in subacute cases not coming under appropriate treatment until late in the disease. Since we have adopted the method of following up a period of intrathecal serum administration with repeated daily lumbar puncture until

PLATE VI.

CHRONIC MENINGITIS IN A YOUNG CHILD.

Illustrating head retraction, flexion of limbs and emaciation.

au.

normal cerebro-spinal fluid is obtained, we have not had one chronic case develop in a patient coming under treatment within the first week.

A special form of chronic meningitis which, owing to its occurring in infants and young children, possesses certain characteristic features is known as the posterior basic type.

Posterior Basic Type of Infants.—This type of case is really a chronic meningococcal meningitis occurring in infants which, owing to the age of the patient, produces a somewhat different clinical picture from that met with in older children and adults. It is most often seen between the ages of four months and two and a half years, but may occur in children up to five years. The condition was originally described by Gee and Barlow in 1878 under the name of "Cervical opisthotonus in infants"; these authors based their observations on 25 sporadic cases, and described the symptoms as being associated with a purulent meningitis at the base of the brain. In 1897, Carr gave a further clinical description, and in 1898, Still isolated from 7 out of 8 cases a diplococcus identical in its main features with those of the meningococcus of Weichselbaum. At that time the condition was thought only to be sporadic, but Koplik, in 1905, established the fact that posterior basic meningitis occurred in epidemic as well as in sporadic form ; of 30 epidemic cases, 8 were of the posterior basic type. Also, the disease shows a seasonal prevalence corresponding with that of cerebro-spinal fever.

The onset is usually sudden, and may be accompanied by a convulsion or screaming ; vomiting is frequent and diarrhoea occurs occasionally. In some cases, the onset is more gradual, consisting of increasing drowsiness and occasional vomiting. The initial temperature varies from 100° to 103° F., but by the end of the first week, pyrexia may be absent ; the temperature then continues normal or slightly above normal for the remainder of the course.

As the disease progresses, the mental condition becomes one of extreme drowsiness, the patient lying quite motionless but with the eyes open and staring. This state of lethargy may be interrupted by an occasional cry. As a rule feeding is not difficult. By the third or fourth day, well marked head retraction is present ; indeed, this is a prominent feature in many patients by the time they come under observation, which, unfortunately, is often late in the disease. As head retraction becomes increasingly well marked, opisthoton   develops, and at times may be so extreme that the

head almost touches the sacrum. Kernig's sign is of no definite value below the age of two years ; the limbs, however, are usually in a condition of spasticity, sometimes being rigidly extended and sometimes flexed. Extreme extension is almost invariable at the ankle joints, and, as a rule, the wrists and fingers are flexed. Periodical and persistent vomiting and progressive emaciation up to an extreme degree are prominent features (*vide* Plate VI.). In infants, the anterior fontanelle bulges, convulsions are frequent, and with increasing hydrocephalus, some separation at the cranial sutures and dilatation of the superficial veins of the scalp may occur.

The later stages are identical with the picture of internal hydrocephalus described elsewhere (Chapter IX. p. 222), associated with marked occipital retraction and opisthotonus. The pupils are dilated and the abdomen retracted. Blindness of central origin is relatively frequent, the optic discs, however, rarely showing any very definite changes.

Lumbar puncture may at first yield a fair amount of cerebrospinal fluid containing meningococci and polymorphonuclear cells. As the condition becomes more chronic, however, the fluid obtained is small in quantity, mononuclear cells replace the polymorphonuclear and organisms cannot be found. " Dry taps " are frequent owing to the development of internal hydrocephalus. If ventricular puncture be performed during life, the fluid obtained may be found to contain meningococci ; organisms have also been demonstrated in the ventricular fluid and exudate at post-mortem examination.

The chronic character of this type of cerebro-spinal fever is illustrated by the statistics of Lees and Barlow ; of 30 cases, the average duration of the course was 7 to 8 weeks. The course may continue for many weeks and in some cases even months. The mortality is over 75 per cent. In cases that recover, permanent blindness, mental impairment, or deafness are frequent sequelae.

Unfortunately, it is uncommon for a patient suffering from the posterior basic type of the disease to come under observation during the initial stages ; consequently, early treatment is seldom possible.

RELAPSES

Most observers differ widely in their statements regarding the relative frequency of relapses. Ker, for instance, records relapses in 15-20 per cent of cases, while Sophian met with a true relapse in

under 5 per cent. Lundie, Thomas, Fleming and Maclagan, in their series, state that early relapses occurred in a "fair percentage," usually at the end of about 14 days; Fairley and Stewart consider relapses rare. The fact is that the "relapses" of some authors are merely the "recrudescences" of others.

A true relapse may be defined as a reappearance of the symptoms and signs of meningitis, including pyrexia, following a certain interval during which they have been absent. There is no doubt that in many cases regarded as relapsing, the meningitis has been only quiescent during the period of apparent recovery. Sophian points out that a slight degree of hydrocephalus, even when accompanied by a cerebro-spinal fluid containing a small number of meningococci, may give rise to a very irregular picture. Pyrexia may be absent and pressure symptoms extremely mild, but more severe symptoms may suddenly appear, together with a rise in temperature. It is important not to confuse such a recrudescence with a true relapse. The patient is never really well during his supposed convalescence, and some objective evidence of meningitis, *e.g.* Kernig's sign, will be present, although subjective symptoms may be almost absent. The cerebro-spinal fluid may appear clear, but it is known that clear fluids, especially in convalescent and chronic cases, may contain a few meningococci. Walking and exercise may permit the meningococci to multiply, thus causing the cerebro-spinal fluid to become turbid and leading to a reappearance of symptoms. A case described by Foster and Gaskell emphasises these views: A patient, after passing through a mild attack of cerebro-spinal fever, had been free from symptoms for 10 days. He was then allowed up and on the following day was seized with headache and vomiting; a considerable quantity of cerebro-spinal fluid was withdrawn. The amount of fluid obtainable on repeated lumbar puncture, however, gradually diminished, and four weeks later he died with all the symptoms of hydrocephalus.

No recurrence of symptoms, therefore, should be considered as constituting a genuine relapse unless at the last lumbar puncture performed, the cerebro-spinal fluid is normal and all symptoms and signs, including Kernig's sign, have been absent for at least two weeks. When these facts are recognised, it will be found that relapses are very infrequent. Goeppert, for example, who did not consider the patient convalescent until Kernig's sign had disappeared, saw the condition only twice in 136 convalescent cases. For our own part, in 150 cases and upwards of 100 convalescents, we have

met with only one true relapse. This occurred in a patient aged 16 years, recovering from an acute attack after 14 days; at the last lumbar puncture of the primary course, the cerebro-spinal fluid was normal both in appearance and pressure and on culture proved sterile. Kernig's sign disappeared about a week later and the patient felt perfectly well. The naso-pharynx, however, continued to yield positive cultures of meningococci. Six weeks after the termination of the first attack a second occurred; this was milder in character than the first, but meningococci were again obtained from the cerebro-spinal fluid, which had resumed its turbid appearance. Evidently, a reabsorption of organisms from the naso-pharynx had taken place, resulting in a true relapse. The patient, however, made a good recovery.

Case XLIV., described on p. 217, might have been regarded as an instance of relapse, but it will be noticed that the patient, when the pyrexia disappeared, still felt far from well, and consequently we preferred to regard his second attack as a recrudescence, a view which was fully borne out by the post-mortem findings.

More than one relapse may rarely occur. Thus, Fairley and Stewart mention one case who had three " distinct attacks " of meningitis within four weeks, each lasting three or four days; they state that in the intervals the patient was afebrile and free from all symptoms and signs of meningitis. The results of naso-pharyngeal swabs are not recorded.

Second attacks of the disease are exceedingly rare but undoubtedly do occur. A case coming under our observation (Case LX. p. 387) had two definite attacks of cerebro-spinal fever at an interval of 13 months, the naso-pharynx being negative 2 months after the first attack.

The method of ensuring against true relapse is clearly to free the naso-pharynx from meningococci as soon as the condition of the patient renders such a procedure possible.

CAUSES OF DEATH IN CEREBRO-SPINAL FEVER

The causes of death in cerebro-spinal fever are as follows:

(1) Toxaemia, especially in fulminating cases.

(2) Sudden respiratory failure. Fairley and Stewart state that in their series of cases, no fewer than 19 died in the acute stage of sudden respiratory failure, According to these authors, this result is not due to hydrocephalus but to cerebral hyperaemia, a general

congestion of the pia-arachnoidal vessels on the surface of the brain, as well as in the vessels throughout the cerebrum and the cerebellum being found at autopsy.

(3) Local cerebral sepsis. Mechanical, as, for instance, in the progressively purulent type.

(4) Hydrocephalus. Increased intracranial pressure.

(5) Secondary broncho-pneumonia.

CHAPTER VIII

COMPLICATIONS

As with other bacterial diseases, complications indicative of a general infection may occur also in cerebro-spinal fever. Meningococcal lesions, distant from the chief seat of infection, are not infrequently met with, *e.g.* arthropathies, pericarditis, endocarditis, etc. In addition, complications such as paralyses and deafness may develop owing to involvement of important nervous structures, nuclei, etc., by the direct extension of the meningeal infection or from excessive intracranial pressure.

In recent years, it must be admitted that serious complications are considerably less frequent than formerly. This is due, no doubt, to the introduction of greatly improved methods of treatment, efficient drainage of the intrathecal space and specific serum therapy, which not only tends directly to inhibit the appearance of complications by overcoming the meningococcal infection, but also by shortening the course of the disease, limits the chances of their occurrence. On the whole, complications are more likely to develop in the more severe cases, but mild cases are by no means immune. Occasionally, although meningitis has ceased, a complication arising late in the course of the disease may retard recovery for a considerable time, *e.g.* pyelitis.

Certain epidemics appear characterised by the frequent occurrence of one particular complication, *e.g.*, pyelitis in the Texas epidemic, 1912. Even in a single epidemic or district, the predominant complication may vary month by month. Apart from those affecting vital organs—pericarditis, pneumonia, internal hydrocephalus—complications cannot be said seriously to affect the general prognosis of the case.

The complications will be dealt with under the headings of the different physiological systems.

GASTRO-INTESTINAL SYSTEM

Haematemesis and Melaena.—Small haemorrhages into the intestinal canal are sometimes met with on post-mortem examination, especially in very acute cases ; clinically, however, haematemesis and melaena are very infrequent. The rare possibility of considerable haemorrhage occurring from the intestine is illustrated by a case mentioned by W. J. Denehy, in which melaena was present ; at the autopsy, the intestinal canal was found to be filled with blood-clot, but no lesion could be detected in the wall of the intestine to account for the condition.

In one case seen early in convalescence, melaena had occurred during the course ; for three weeks prior to the onset of cerebro-spinal fever, however, the patient had complained of dysenteric symptoms—diarrhoea and the occasional passing of mucus and blood. Beyond this, in over 160 cases, no melaena occurred.

Vomiting and Diarrhoea occurring during the course of the disease have already been dealt with (*vide* Chapter VI. pp. 76-77). Jaundice is rare ; it was present in 1 per cent of Fairley and Stewart's cases but was not encountered in our own series.

Cholecystitis has been described, but the condition was not due to the meningococcus.

Parotitis.—Inflammation of a salivary gland is a rare event in cerebro-spinal fever. Suppurative parotitis is mentioned by H. D. Rolleston as occurring in one of 163 cases.

CARDIO-VASCULAR SYSTEM

Pericarditis.—This condition may be present as a complication in acute cases. In our experience it has occurred only in those of the acute fatal type (*vide* p. 144), dying within six or seven days of the onset of the disease. As a rule, pericarditis is first discovered only upon post-mortem examination, weak heart sounds and stertorous breathing rendering diagnosis almost impossible during life. In our cases, the exudate was invariably fibrino-purulent. Although meningococci have been seen in films of the exudate, their demonstration is exceptional. Serous pericarditis is of extremely rare occurrence.

Of 276 cases occurring in the Royal Navy from August 1914 to August 1916, commented upon by H. D. Rolleston, pericarditis is mentioned as occurring in 6 ; of these, 3 cases recovered.

Fairley and Stewart mention a case showing suppurative mediastinitis involving the pericardium ; Gram-negative diplococci were isolated from the pus.

Myocardial Changes.—The temporary cardiac dilatation which may occur in acute cases has already been described among the symptoms of the disease (*vide* p. 91). It is probably due to the occurrence of cloudy swelling, as this condition, accompanied by some dilatation of the heart cavities, is almost invariably found upon post-mortem examination in cases dying during the first two weeks of illness.

In cases recovering, the heart usually returns to the normal, the quickened pulse also resuming its normal rate with the patient's general improvement. In rare instances, however, tachycardia may persist long after convalescence. We have met with one such case.

CASE XXV.—The patient, aged 25 years, being a subacute case, was not received into hospital until the 13th day of illness. The disease ran the long course of about 48 days before finally terminating in recovery.

On the patient's admission, the apex beat was one inch internal to the nipple line and the cardiac sounds were normal. Until the 20th day of observation (32nd day of disease), the pulse rate averaged 80-90 per minute ; from this time onwards, however, it gradually increased to 100-120, finally persisting at a continuous level of between 110 and 120. On the 40th day of illness, the apex beat was $\frac{1}{2}$ inch internal to the nipple line, but the cardiac sounds remained normal. The tachycardia continued after the termination of the course of meningitis, the cerebro-spinal fluid being clear and normal on the 46th day of illness.

When examined a month later, in spite of continuous rest in bed, the patient showed a pulse rate varying between 100 and 120 ; the apex beat remained $\frac{1}{2}$ inch internal to the nipple line. He was then transferred to a convalescent hospital where he was allowed up, and when seen two months later, that is, three months after the termination of meningitis, he exhibited a pulse rate varying between 120 and 140. The apex beat was about $\frac{1}{4}$ inch internal to the nipple line and the sounds were still normal. The patient complained of considerable palpitation, dyspnoea, and weakness in the legs on walking even a short distance.

Myocardial changes, leading to irregularities of the cardiac beat, are of extremely rare occurrence. One such case appears in our series.

CASE XXVI.—In a subacute case, aged 37 years, admitted to hospital on the third day of illness and exhibiting a turbid cerebro-spinal fluid

containing meningococci, the pulse was found to drop a beat about twice per 100 beats, the pause occurring at irregular intervals. This condition persisted throughout the course of 32 days, the patient recovering in spite of an intercurrent attack of lobar pneumonia making its appearance on the 13th day. The pulse rate varied between 80 and 96 per minute until the onset of pneumonia, when it rose to continue between 104 and 134. With the pneumonia terminating by crisis on the 22nd day, the pulse again resumed its previous rate. Notwithstanding the acceleration during the pulmonary complication, the pulse continued to drop a beat with the same relative frequency. As stated above, there was no regularity in the occurrence of the pause ; it was noticed about twice per 100 beats, with a rough average of 1 in 40. On the patient's admission to hospital, the apex beat was one inch internal to the nipple line, the cardiac dulness corresponding, and from this there was no apparent change throughout the course. On auscultation, the pauses at the wrist were clearly due to the existence of a premature extra-systole, the ordinary sounds being normal.

The above condition was still present two weeks after recovery. Nothing definite was known concerning the previous state of the heart, but the patient, an intelligent and educated man, was not aware that he had dropped an occasional cardiac beat prior to his illness, nor had he had any other acute illnesses. When seen three months after recovery from cerebro-spinal fever no cardiac irregularity could be detected.

Although it is to be regretted that no polygraph or electro-cardiograph was available, there can be no doubt of the extra-systole ; we suggest that it was possibly due to a focal myocardial lesion eventually clearing up.

In 1915, J. D. Windle reported a subacute case, confirmed by bacteriological examination of the cerebro-spinal fluid, in which " escape of the ventricle " occurred. The patient, aged 15 years, at first showed a regular pulse varying in rate between 80 and 90 per minute ; with increasing drowsiness, however, it dropped to 60 and became irregular. Two polygraph tracings, taken at some hours' interval on the same day, showed frequent fusion of the " a " and " c " waves into one of greatly increased amplitude, with an arrhythmia due to " nodal " extra - systoles. The second and later tracing shows these " nodal " extra - systoles to have become more numerous than when the earlier one was recorded. Windle suggests that the irregularity was due to involvement of the vagus centres, but we are inclined to the view that the condition was probably myocardial and that the a-v node was involved to a certain extent by some irritative lesion. Similar arrhythmia, progressing to true " nodal rhythm," has already been described in detail, with its

pathological basis, by one of us (A. M. K.). In many acute infections, including cerebro-spinal fever, cellular inflammatory foci are frequently met with in the cardiac musculature. If these should involve the primitive tissues, a corresponding disturbance of rhythm results. In Windle's case, there were probably foci in the cardiac muscle, some of which affected the a-v node and irritated it, the irritation increasing with the progress of the lesion.

Myocarditis, leading to auricular fibrillation without valvular change, occurred in one of Foster and Gaskell's cases ; the previous condition of the heart, however, was doubtful.

Here it may be mentioned that, in addition to cloudy swelling, the myocardium, on post-mortem examination, may show inflammatory and degenerative lesions. Westenhoffer has described diffuse and circumscribed infiltration of the cardiac muscle.

Accompanying endocarditis, there may also be a considerable degree of myocarditis.

Endocarditis.—Ulcerative endocarditis, due to the meningococcus, may occur in rare instances as a complication. Wright MacKarell records two cases in which the mitral valve was affected. The first of these had a comparatively short attack of meningitis, clear cerebro-spinal fluid being obtained within six days of the patient's admission to hospital. Subsequently, however, meningococci were obtained on blood culture, and murmurs developed in the mitral area ; eventually, the patient died $12\frac{1}{2}$ weeks after the primary onset. In the second case, endocarditis was discovered only upon post-mortem examination ; death occurred after a course of sixteen weeks' duration, the cerebro-spinal fluid having yielded meningococci in culture. In both cases, large vegetations were found on the mitral valves, and sections of the vegetations showed the presence of numerous Gram-negative diplococci.

Fairley and Stewart also mention two cases, one of which exhibited evidence of pre-existing valvular disease of the heart ; on post-mortem examination, fresh vegetations were found implanted on old sclerosed mitral and aortic valves. In the second case, two cusps of the aortic valve were affected with fresh vegetations, cultures from which yielded meningococci. Two further instances have been reported by Westenhoffer, in both of which the mitral valve was affected. The first patient, aged one year, ran a course of three weeks' duration ; the second, aged 21 years, died after five days' illness. In both cases, autopsy revealed suppurative meningitis, with fresh vegetations on the mitral valves.

Although we met with no case of endocarditis complicating meningitis, one case of primary meningococcal septicaemia with ulcerative endocarditis, due to the meningococcus, occurred in our series. This case (Case LIX.) is fully described on p. 347.

Phlebitis.—This is an uncommon complication. Most frequently the veins of the lower extremities are affected, although Sophian has seen phlebitis of the jugular and deep thoracic veins. In our series it occurred in one case only; the veins of the left leg were involved, and subsequently led to oedema of the limb. It had not completely disappeared three months after recovery.

Embolism.—Embolism, leading to pulmonary and splenic infarcts, may occur in association with ulcerative endocarditis. Fairley and Stewart record a case in which embolism and consequent occlusion of the axillary artery occurred following the appearance of endocarditis of the aortic valve.

Haemorrhage.—Haemorrhages have been described according to the particular organ affected by the complication. Thus, the following haemorrhages may occur :

> Purpuric rash (p. 95).
> Epistaxis (p. 92).
> Melaena (p. 179).
> Haemorrhage affecting serous membranes.
> Pulmonary haemorrhage (2 cases, Denehy).
> Haematuria (p. 100).
> Haemorrhage into the adrenal bodies (pp. 140, 365).
> Cerebral haemorrhage (p. 204).
> Subarachnoid meningeal haemorrhage.
> Haemorrhage into the subarachnoid space (blood in cerebrospinal fluid, not always due to lumbar puncture—p. 241).

LYMPHATIC SYSTEM

Although tenderness in the submaxillary region may be demonstrated very early in the disease, any considerable glandular enlargement is uncommon. In only one of our cases did marked cervical adenitis develop, and it was then late in the disease.

Case XXVII.—The patient, aged 25 years, had had a sudden and abrupt onset consisting of headache followed by a feeling of soreness in the throat and later by vomiting. On admission to hospital, he was found to be suffering from subacute cerebro-spinal fever; the tonsils were slightly inflamed, and there was some injection of the pharyngeal

wall.   These symptoms rapidly disappeared as the patient improved.
On the 18th day of illness, however, a large swollen gland was discovered
on the left side, behind the angle of the jaw and under the sterno-mastoid
muscle ; the throat was quite normal in appearance.   Also, the menin-
gitis had steadily improved and neck rigidity was only slight.   On the
24th day, the swelling of the gland had disappeared, and by the 30th
day the cerebro-spinal fluid was clear and normal.

In Fairley and Stewart's cases, several convalescent patients
showed marked cervical adenitis, appearing during the first week
after recovery.   In some cases the salivary glands were also affected,
but no tendency to pus formation was observed, the swellings sub-
siding slowly under fomentations.

Spleen.—The spleen is occasionally somewhat enlarged in acute
cases, but such enlargement is never sufficient to allow its being
demonstrated clinically.   In cases complicated by ulcerative endo-
carditis, the organ may be the site of infarction.

RESPIRATORY SYSTEM

Pneumonia.—Pneumonia is a somewhat frequent complication,
occurring in about 10 per cent of all cases.   It may often appear
while the patient's general condition is good ; also, it develops as
a terminal affection.   The mortality among cases exhibiting this
complication is heavy ; in Sophian's series of cases, 90 per cent of
patients with pneumonia died.   Of our own cases only one recovered.
Hypostasis at the bases of the lungs, which readily occurs in un-
conscious patients owing to gravitation and congestion, is an
important predisposing factor.   Consequently, patients should not
be allowed to lie in a supine position for many hours without the
position being changed from time to time.

Broncho-pneumonia.—This condition is not uncommon, being
relatively more frequent in children than in adults.   It usually
appears in the more acute cases and is almost invariably fatal.
Hypostatic congestion is a most important predisposing cause.
Also, in our experience, the patients developing broncho-pneumonia
were usually those in whom a more or less sudden onset of cerebro-
spinal fever was preceded by a period of malaise consisting of a
" cold " or " cough " ; not infrequently, they presented catarrhal
symptoms on admission to hospital.   As an example, the following
case had just recovered from an attack of bronchitis, when suddenly
he developed cerebro-spinal fever in a severe form ; although the

meningitis improved, broncho-pneumonia supervened and the case terminated fatally.

CASE XXVIII. (Fig. 4, p. 78).—A youth, aged 18, was admitted to a general medical ward for severe cough of one week's duration. His temperature was 101·2° F., pulse 92, and respirations 24. He had a short and sharp cough with somewhat loose expectoration, and scattered râles and rhonchi were heard on both sides of the chest ; these signs were rather more numerous in the lower lobe of the right lung. The patient improved rapidly, and three days later the temperature was normal and the chest apparently clear. On the morning of the following day, he said that he felt quite well, and at mid-day sat out of bed for a short time. At 2.30 P.M., however, the patient started shivering and exhibited two or three definite rigors. During the evening he complained of intense headache, the temperature in the meantime having risen to 103° ; about 10 P.M. vomiting occurred. His mental condition at this time was stated to have been perfectly normal. During the night delirium supervened, and several times he tried to get out of bed.

On the following morning, the patient was unconscious and profoundly collapsed, being very pale and almost pulseless ; a petechial rash of almost universal distribution, with occasional purpuric spots, was present on the limbs and trunk and even on the face. Owing to the collapse, a considerable degree of muscular flaccidity occurred, neck rigidity being only very slight and Kernig's sign absent. The lungs appeared clear. Lumbar puncture yielded 60 c.c. of turbid fluid containing numerous meningococci.

With active stimulation and the intrathecal administration of serum, the patient's condition gradually improved, until, on the 3rd day, he was able to take nourishment well and exhibited periods of normal consciousness alternating with intervals of delirium ; at times he answered questions rationally. On the same day, however, mucous râles developed in both lungs, more especially in the lower lobes. In the meantime, neck rigidity and Kernig's sign had become well marked. On the following day (4th), although the patient appeared rather more conscious, incontinence of urine was present and the mucous râles more numerous. During the afternoon the respirations rose from 34 to 60 per minute ; the temperature also reached 103·2°, being the highest temperature recorded since the day of onset. The pulse rate, previously 100-130, remained at about the same level. On the 5th day numerous crepitations were heard over the lower lobes of both lungs, and, in addition, there was some patchy bronchial breathing at the right base ; no marked impairment of resonance, however, was present. The same evening, the patient became comatose and died a few hours later.

The cerebro-spinal fluid remained turbid throughout the course, meningococci also persisting ; in the cerebro-spinal fluids obtained at the later lumbar punctures, however, the organisms were less numerous. Post-mortem, in addition to purulent meningitis, the lungs showed

general oedema and marked bronchitis with muco-purulent exudate. In the lower lobe of the right lung, there were a few patches of broncho-pneumonia.

A terminal broncho-pneumonia is frequent in cases of the acute fatal and progressively purulent types. Owing to the extremely weak respirations, the clinical diagnosis of this complication is often difficult. A sudden rise in the respiratory rate, together with a diminishing pulse-respiration ratio, is a significant sign, but as this sometimes occurs during the coma that precedes death, the change is not conclusive.

Lobar Pneumonia.—This is somewhat infrequent. We met with only two instances in 160 cases ; its average frequency is said to be about 4 per cent. The condition is illustrated by the following case :

CASE XXIX. (Fig. 28).—A subacute case, aged 37 years, was admitted to hospital on the third day of illness. Mentally, he was somewhat dull and lethargic, taking little or no interest in his surroundings, but answering questions well when roused. A macular rash was present over the lower limbs and chest, and herpes was beginning to appear on the lower lip. Neck rigidity and Kernig's sign were both well marked. The lungs appeared normal. On lumbar puncture, 40 c.c. of turbid fluid were obtained, which contained a few meningococci.

Under serum treatment, etc., the patient progressed satisfactorily until the evening of the 13th day, when the respirations were noticed to vary somewhat in depth and rhythm ; the respiratory rate, never before above 28 per minute, had also increased from 24 to 40, and the pulse rate from 84 to 120 (P/R ratio from 3·5 to 3). During the evening, the temperature reached 103·4° F., the highest recorded during the whole course. On examination of the chest, impairment of resonance, together with considerable diminution in breath sounds, was found over the lower lobe of the left lung. On the following day, the respirations were frequently irregular, the percussion note over the left lower lobe was still further impaired, and there were several small areas of bronchial breathing. These latter areas became more extensive and coalesced towards the 18th day (5th day of pneumonia). On the 20th day, no bronchial breathing could be detected in the affected lobe ; impaired resonance, however, continued with somewhat diminished breath sounds and increased voice sounds. Films of the serum obtained by lung puncture showed pneumococci, no meningococci being detected. The sputum contained pneumococci and both Gram-negative and Gram-positive cocci.

From the 22nd day, when the pneumonia terminated after a course of nine days, the lung cleared rapidly and was quite normal by the 28th day.

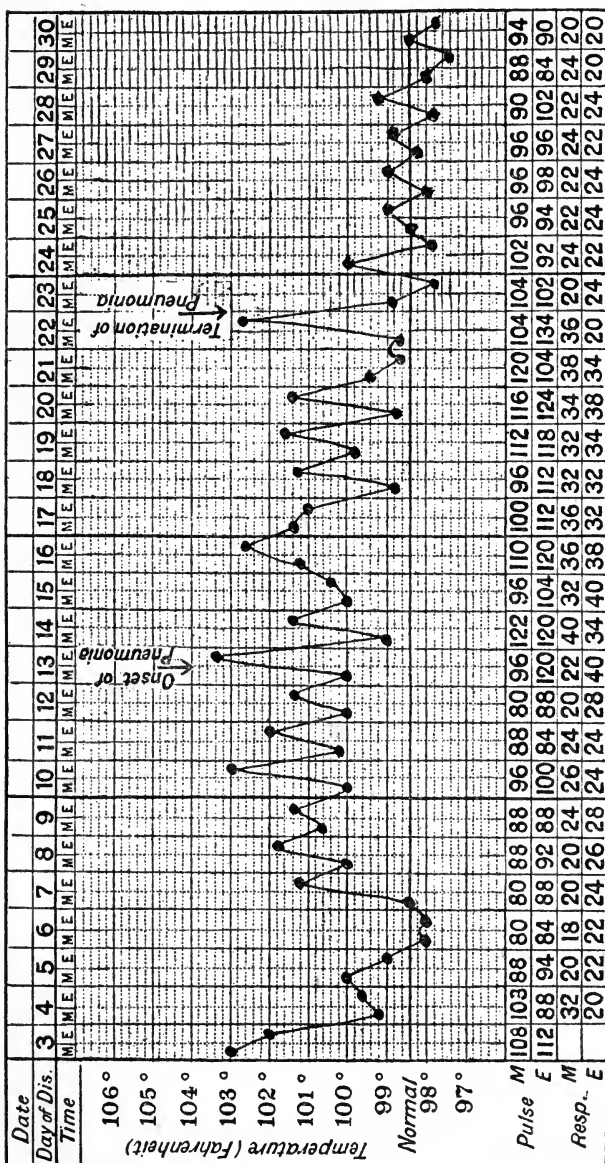It will be seen by the temperature chart (Fig. 28) that, during

Fig. 28.—Subacute case of Cerebro-spinal Fever developing lobar pneumonia on the 13th day of illness and terminating in recovery. (Case XXIX. p. 186.)

the course of the pneumonia, pyrexia was irregularly remittent, the evening temperature being higher than that recorded in the morning. On the 22nd day it fell from 103° to 98·8° and did not rise again above

100° ; similarly, the respiratory rate dropped from 38 to 20 per minute. The pulse rate, however, diminished more gradually.

While pneumonia was in progress, the meningitic symptoms had slowly improved, no meningococci being visible in the cerebro-spinal fluid after the 25th day (3 days after the termination of pneumonia) ; on the 31st day the cerebro-spinal fluid was quite clear and normal.

As regards treatment, anti-meningococcal serum was administered intrathecally until the 12th day, after which lumbar puncture alone was employed. Vaccine was also given every four days, from the fifth day onwards, in doses increasing from 250 millions to 2500 millions.

The appearance of an intercurrent pneumonia while meningitis is improving, may lead to a recrudescence in severity of the latter condition, and one to which the patient succumbs. The recrudescence is permitted, no doubt, by a further diminution in resistance to the meningococcus, owing to the lowering of the general vitality in turn brought about by the development of pneumonia. This occurrence is illustrated by the following case, in which the course of pneumonia was remarkably short :

CASE XXX. (Fig. 29).—The patient, a man aged 60 years, was admitted unconscious, with retention of urine and well-marked stertorous breathing. The onset of the disease had occurred suddenly, following a " cold " and " sore throat " of about one week's duration. On account of his age, he was at first regarded as a case of cerebral haemorrhage and admitted to a general medical ward ; it was not until the third day of illness, therefore, that lumbar puncture revealed the true nature of his malady. On the following day (4th), though very deaf, he was more conscious. During the next two days his mental condition became clearer and retention of urine passed off ; also, meningococci were found to have disappeared from the cerebro-spinal fluid obtained on lumbar puncture. From this time until the 13th day, the patient's consciousness was normal and the deafness had improved considerably.

During the evening of the eighth day pneumonia supervened, the respiratory rate rising from 24 to 34 per minute and the pulse from 90 to 106 (P/R ratio from 3·75 to 3·1). Impaired resonance was discovered over the lower lobe of the right lung on the following morning, together with crepitations and bronchophony. On the 10th day there were areas of bronchial breathing. By the 12th day, however, this latter sign had disappeared, the breath sounds being weak and a few crepitations persisting. On the 14th day (6th day pneumonia), there was still some impairment of resonance at the right base, but no crepitations or other physical signs. In the meantime, accompanying the reappearance of meningococci in the cerebro-spinal fluid, increased meningitic symptoms had developed on the 12th day ; delirium and incontinence followed, and on the 14th day he relapsed into coma, the

pneumonic condition having practically cleared. Death occurred on the 16th day of illness. Post-mortem, the lower lobe of the right lung showed resolution well advanced.

A primary meningococcal pneumonia has been described by some authors. Thus, Sophian mentions a case of pneumonia, occurring in a woman, whose sputum showed the presence of numerous meningococci; after four days she developed meningo-
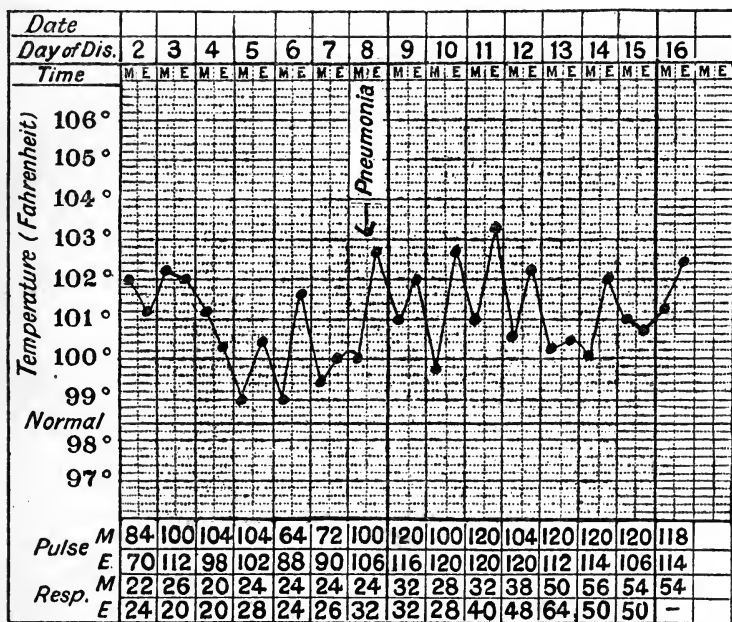

FIG. 29.—Case of Cerebro-spinal Fever, in which meningitis was progressing favourably, developing pneumonia on the eighth day. Although the latter condition improved, a recrudescence of meningitis occurred which led to a fatal termination. (Case XXX. p. 188.)

coccal meningitis. Jacobitz has described an epidemic in which pneumonia, said to be due to the meningococcus, was present in all the cases. Also, Fairley and Stewart describe a case, aged 18 years, who was admitted to hospital with pyrexia (103·2° F.), pulse 120 and respirations 48; he was drowsy and lumbar puncture yielded 20 c.c. of clear fluid. Two days later, apical consolidation, with dulness and tubular breathing, of the right lung appeared. After two further days the whole lung was solid. On the sixth day the patient developed meningitis; on lumbar puncture, a turbid fluid was obtained which yielded Gram-negative diplococci in culture.

The patient died on the seventh day of illness. The above authors state definitely that they regard this case as a meningococcal septi-caemia with localisation in the lung and a terminal meningitis. The evidence for such an assumption, however, we must regard as insufficient; there is nothing, indeed, to show that the pulmonary condition was not pneumococcal. In our opinion, it cannot be too strongly urged that the mere presence of pneumonia, either preced-ing or occurring during the course of a meningococcal meningitis, is no proof that the pneumonia is due to the meningococcus. Should Gram-negative cocci, with the apparent morphological characters of the meningococcus, be detected in the sputum, such organisms, even if they were meningococci and not micrococcus flavus or catarrhalis, might well have been derived from the naso-pharynx.

Of somewhat more significance is a case of lobar pneumonia reported by Heiman and Feldstein, in which meningococci were cultivated from the blood stream as well as from the cerebro-spinal fluid. Lung puncture and examination of the serum withdrawn, however, is the only certain method of proving the exact nature of the causative organism in a suspected meningococcal pneumonia. The few cases in which this has been done, as far as we are aware, have yielded pneumococci and not meningococci (vide Case XXIX. p. 186).

Bronchitis.—A slight degree of bronchitis exists in a certain pro-portion of cases (10 per cent); it is more frequent in those proving fatal. In cases recovering, the physical signs, appearing about the fourth day, are usually limited to a few scattered rhonchi; the cases exhibiting numerous moist râles often develop broncho-pneumonia.

In many cases, purulent bronchitis may be found at autopsy.

Pleurisy.—This condition occurs only in association with pneumonia. It may be manifest by serous effusion or, more rarely, empyema.

Sinusitis.—Empyema of the bony sinuses may occur, the sphenoidal sinus and ethmoidal cells usually being involved. Owing to the difficulty of clinical diagnosis, the condition is discovered, as a rule, only upon post-mortem examination; the exudate may contain meningococci, but occasionally the infection is mixed. Embleton and Peters describe a recrudescent case in which, during life, the sphenoidal sinus was opened from the nose, a drachm of pus escaping; on examination, this pus showed meningococci. The patient made a good recovery.

In 29 autopsies, Westenhoffer found that 34 per cent showed

some inflammation of the sphenoidal sinus.   These results led him to advocate the view that the usual mode of invasion of the meninges by the meningococcus was by direct extension ·from the naso-pharynx to the sphenoidal sinus ; from the latter, it was assumed that inflammation could readily spread through the thin lamina . of bone separating the sphenoidal sinus from the cranial cavity. Further observations, however, led Westenhoffer to abandon his former view ; he was unable to demonstrate meningococci in the bone itself, and found that the exudate was confined to the superior and lateral aspects only of the bone (*vide* Chapter V. p. 59).

Fairley and Stewart mention two cases of cerebro-spinal fever in which inflammation of the antrum of Highmore was found.

Hiccough.—In association with retention of urine, hiccough may occur ; it was observed by us in two progressively purulent cases and ceased soon after catheterisation of the bladder.

On post-mortem examination, multiple haemorrhages into the lungs may occasionally be found in fulminating cases ; haemoptysis, however, is exceedingly rare.   Infarction of the lung may occur in cases complicated by endocarditis.

URO-GENITAL SYSTEM

Pyelitis.—This complication appears to be frequent in some epidemics while in others it is rare or absent.   Of our own series, no definite case of pyelitis occurred, although pyuria, as shown by the presence of pus cells in the urine, was noted in about 30 per cent of cases ; it was unassociated with any definite urinary symptoms. In the Texas epidemic of 1912, Sophian estimated that pyelitis occurred in 5 per cent of cases, being most frequent in those severely ill.   Examination usually elicited tenderness over the kidney and ureter ; occasionally enlargement of the kidney could be demon-strated.   The urine was purulent and is said to have contained many meningococci.

The pyelitis complicating cerebro-spinal fever is of a benign order and never develops into a true surgical kidney.   It may sometimes be the cause of persistent pyrexia after recovery from meningitis.

Cystitis.—Cystitis is not uncommon in those patients in whom, owing to persistent retention of urine, continued catheterisation is necessary.   Apart from these cases, however, cystitis may occur.

Usually, the colon bacillus is the responsible organism, but occasionally B. proteus or a staphylococcus ; in no case of ours were meningococci obtained. Sheffield Neave twice found the latter organisms as the cause of a complicating cystitis, but later they were replaced by the bacillus coli or staphylococci. MacMahon also records the case of a soldier suffering from a severe attack of cerebro-spinal fever who developed purulent cystitis with abundant meningococci in the urine.

Nephritis.—This condition, occurring as a complication of cerebro-spinal fever, has received but little attention. When evidence of nephritis is observed, the possibility of pre-existing renal disease must, of course, be borne in mind.

Nephritis was present in five cases of our series ; in two patients, at least, it existed prior to the attack of cerebro-spinal fever, and probably also in another. In such cases the prognosis appears to be unfavourable. The two remaining patients furnish some ground for the belief that a mild nephritis may occur as a direct complication of cerebro-spinal fever.

Cases in which Nephritis existed prior to the Development of Cerebro-spinal Fever

Case XXXI.—For two years previously the patient, aged 24 years, had complained of palpitation and dyspnoea on exertion ; it had been ascribed to a " weak heart." The onset of cerebro-spinal fever was abrupt, and the case proved to be a progressively purulent type, death occurring on the ninth day of illness. Slight albuminuria was present throughout the course, together with the presence in the urine of both hyaline and granular casts.

Post-mortem, the capsules of both kidneys were somewhat adherent, and on being stripped, left a finely granular surface ; in addition, there was well-marked cloudy swelling. There was no marked thickening of the arteries. The heart showed hypertrophy of the ventricles with slight dilatation of all four chambers.

Case XXXII.—The patient, aged 28 years, had a history of previous dyspnoea on exertion and frequency of micturition. This case also was of the progressively purulent type, and proved fatal on the seventh day of disease. Albuminuria, varying from 1 to 0·5 per cent (Esbach), was present throughout, occurring with a smoky urine containing blood. On microscopical examination red blood cells, hyaline, granular and blood casts were found to be present. No autopsy was obtainable.

Case XXXIII.—The patient, aged 22, was known to have had an attack of acute nephritis six months prior to his developing cerebro-spinal fever. The onset of the latter was peculiar in that a further

attack of acute nephritis developed immediately prior to meningitic symptoms. He first complained of pain in the lumbar region ; two days later marked albuminuria was discovered, followed next day by intense haematuria. The latter condition persisted, and six days later the patient suddenly developed severe headache and vomiting. He came under our observation on the fifth day of cerebro-spinal fever. The usual signs of meningitis were well marked, and lumbar puncture yielded a turbid fluid exhibiting meningococci both on direct microscopical examination and on culture. Intense haematuria was present, and the urine exhibited, in addition to blood cells, numerous hyaline and granular casts ; cultures from catheter specimens proved sterile.

After the tenth day of disease the signs of meningitis, under specific treatment, rapidly improved, and on the 17th day the cerebro-spinal fluid was quite clear and sterile. Haematuria, present throughout the course of meningitis, persisted for the first two weeks of convalescence ; following this, the amount of blood in the urine gradually decreased until six weeks after recovery from meningitis, there existed only a faint trace ; numerous leucocytes and granular casts, however, were still present. The urine was examined bacteriologically every third day throughout the course of illness, but at no time were meningococci observed. Casts continued to be present when the patient had regained his usual health.

Cases in which Nephritis was probably a direct Complication of Cerebro-spinal Fever

Case XXXIV.—The patient, aged 18 years, had had no previous illnesses. The case was acute, but terminated in recovery after the short course of nine days. On the second day of illness, the urine showed a specific gravity of 1030, acid reaction, and albumin present to the extent of 0·4 per cent (Esbach). On microscopical examination, red blood corpuscles, leucocytes and epithelial casts were seen but no organisms. This condition persisted until the 8th day, together with considerable frequency of micturition. From this point onwards, however, the urine cleared rapidly, and within a few days of obtaining a clear cerebro-spinal fluid on lumbar puncture, it was quite normal. Weekly examination during convalescence failed to show any further abnormality.

Case XXXV.—The patient, aged 18 years, came under observation on the third day of an apparent recrudescent attack of meningitis. From the 6th day (41st of total illness) the patient showed frequency of micturition and a urine, specific gravity 1025, containing 0·5 per cent albumin, together with blood cells, renal epithelial cells and hyaline casts. Death occurred three days later. At autopsy the kidneys showed considerable cloudy swelling, and the catarrhal line around the bases of the pyramids was exceedingly well marked.

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Among a series of 161 cases of cerebro-spinal fever, Bourke, Abraham and Rowlands mention nine as showing evidence of nephritis; one patient exhibited oedema of the face and the dependent parts. Of the nine cases, four died and five recovered; the latter continued to show a slight albuminuria, associated with the presence of hyaline and granular casts. No mention is made, however, of the previous history of these patients.

Multiple abscesses of the kidney are occasionally seen; meningococci have been demonstrated in such foci by Ghon and Weichselbaum. In Fairley and Stewart's series, pyelo-nephritis with multiple abscesses was observed in two cases; in both instances it was associated with cystitis.

Epididymitis.—This is a somewhat infrequent complication. It occurred in four of a series of 160 cases; in each instance it was not apparent until the first few days of convalescence. In one case only had a catheter been used in the early stages of the disease, and then only twice; the other three cases were subacute. No case showed any accompanying rise in temperature or pulse rate. The condition was unilateral, and the swelling and tenderness affected chiefly the globus major; intermittent pain was frequently complained of. In all cases the urine was normal; one patient only had showed some albuminuria during the first few days of illness. The inflammation eventually subsided in 10 to 20 days.

Of 410 cases of cerebro-spinal fever occurring in the Royal Navy from August 1, 1914, to July 31, 1917, summarised by H. D. Rolleston, orchitis or epididymitis occurred in eight. In a case recorded by Pick—that of a boy aged 18 years—double empyema of the seminal vesicles was found at autopsy, the bladder, testes and vas deferens being normal. The pus from the vesicles yielded meningococci, the nature of the organism being proved by sugar and agglutination reactions.

ARTICULAR SYSTEM

Arthropathies.—In most epidemics 10 to 15 per cent of the cases have developed arthropathies; recently, however, they seem to have occurred rather less frequently, *e.g.* of 410 cases occurring in the Royal Navy from August, 1914, to July 31, 1917, commented upon by H. D. Rolleston, 20 showed arthropathies (4·8 per cent); of 200 cases, Netter and Durand found joint lesions in eleven (5·5 per cent). In our own series of cases arthropathies developed in only 3 per cent.

The joints may frequently become involved during the acute

stage of the disease, usually on or about the fourth day of illness, but occasionally the lesion may not develop until towards the end of the course.   One or more joints may be implicated ; in the latter case both small and large joints are often attacked simultaneously. Netter and Durand mention the case of an infant in which thirteen joints were involved.   The knee and shoulder joints are probably those most frequently affected, but almost any joint may become attacked—elbows, wrists, hips, ankles and even the smaller joints of the fingers and toes.

The lesion appears to be a synovitis rather than a true arthritis. Unlike gonorrhoeal arthritis, invasion of the periarticular tissues, leading to adhesions or ankylosis of the joint, is exceedingly rare. Occasionally a secondary staphylococcal infection may occur, resulting in the destruction of joint structures.

At first the joint is hot and tender to the touch, but redness of the entire skin about the joint is rare ; erythematous patches, however, may appear.   Spontaneous pain is not a prominent feature, and the patient as a rule is aware only of the swelling.   Fluid can readily be detected in the joint but the amount is seldom excessive.

Not infrequently the arthropathy is merely transitory, the effusion disappearing within a few days, leaving the joint apparently normal.   At other times, however, the joint becomes tense and the lesion is more persistent ; Sophian mentions cases in which arthropathies were still active four months after their appearance.

Upon aspiration, the joint effusion is usually found to consist of a thin purulent fluid containing numerous polymorphonuclear cells. Gram-negative diplococci may be present, but, in our experience, are more often absent both on direct microscopical examination and on culture.   Occasionally the effusion returns temporarily after aspiration.

The following example illustrates the occurrence of arthropathies in an acute case which eventually terminated fatally on the thirty-first day of illness.

Case VI. (also p. 84).—A patient, aged 24 years, was admitted to hospital on the second day of disease, profoundly delirious and showing a well-marked petechial rash with occasional purpuric spots and patches. He remained more or less delirious until death on the 31st day.   On the fourth day, redness and swelling was noticed round the third meta-carpo-phalangeal joint of the right hand ; by the seventh day this had disappeared.   On the evening of the fifth day fluid was detected in the left knee joint ; exploration yielded a purulent fluid containing

pus cells, but no organisms were seen in films, and cultures remained sterile. By the eighth day the left knee was practically normal, but the effusion reappeared on the ninth; exploration gave the same result as before, no organisms being seen or cultivated. By the twelfth day the left knee was again normal. On the eighth day, that is three days after the appearance of infection in the left knee joint, the right knee was also found to contain fluid; exploration showed a purulent fluid similar to that obtained from the left knee—it contained pus cells but no organisms were seen or cultivated. The right knee was normal on the eleventh day.

In rare instances, an arthropathy has been the first apparent indication of a meningococcal infection. Soloman, in 1902, reported the case of a woman, aged 30, who developed " chills " and fever which were followed by pain and swelling of the elbow, knees, and joints of the hand. Blood culture yielded meningococci. Pyrexia, etc., persisted for two months, the case in general presenting the appearance of a severe sepsis. The patient then developed meningitis, meningococci being present in the cerebro-spinal fluid; ultimately, however, she recovered. Sophian also mentions a case, that of a woman who developed what appeared to be an attack of acute articular rheumatism affecting both large and small joints. Three weeks later, while several of the small joints were still inflamed, meningitis appeared, meningococci being obtained from the cerebro-spinal fluid. Under specific serum treatment the meningitis improved and some of the joint lesions disappeared. During convalescence, however, one of the shoulder-joints, which had previously been affected, became steadily worse; aspiration yielded a purulent fluid containing many meningococci. Sophian considers it probable that from the outset the joint condition was due to the meningococcus. Further, cases of swollen joints have been met with in which the lesion was apparently meningococcal, although the patient never developed meningitis (*vide* Chapter XIV. p. 352).

Prognosis, as regards the joint lesion, is good; some observers, indeed, have considered the occurrence of arthropathies as a sign favouring recovery of the patient. Nevertheless, many cases developing such lesions terminate fatally, and we cannot say that in our experience the appearance of an arthropathy has any definite prognostic value.

Synovitis may also occur as one of the manifestations of " serum disease " and care must be taken not to mistake it for an arthropathy. The condition with its associated symptoms is fully described in the section dealing with serum disease (Chapter XIX. p. 462).

SKIN

Bed-sores are extremely liable to occur in subacute and chronic cases associated with the rapid wasting. Consequently, every care must be taken to prevent their appearance (*vide* Treatment, p. 445).

Carbuncles may occasionally be present but are staphylococcal in origin. A curious raised patch sometimes affecting the region of the buttock has already been mentioned (p. 96).

NERVOUS SYSTEM

Hemiplegia.—This complication is not common but may appear both in acute and subacute cases and often late in the disease. In some cases it is transitory, lasting only about thirty-six hours ; in others it may be more permanent.

Hemiplegia developed in one case of a recrudescent type of our series—that of a boy aged 15 years (Case XXII. p. 164). Several recrudescent rises of temperature occurred during the long course of eleven weeks before he finally recovered from the meningitis. The paralysis appeared to follow one of these pyrexial crises—the temperature, which had been normal for three days, suddenly rose to 103° during the afternoon of the 50th day ; severe headache preceded and accompanied the rise. At the same time the cerebro-spinal fluid obtained by lumbar puncture was turbid and yielded a good growth of meningococci. On the day following (51st), paralysis of the left arm was present, the limb being held across the body, flexed at the elbow and the palm towards the chest in the position typical of an upper neurone palsy. No voluntary movement was possible at the shoulder, elbow or wrist, but fair movement remained in the fingers. The biceps showed some spasticity and the supinator, biceps and triceps jerks were all brisker than those on the opposite side. The electrical reactions were unaffected.

The leg had not yet become involved, the tendon reflexes of each side being equal and the plantars flexor. Next day (52nd), however, weakness appeared in the limb—he was able to perform all movements but they were diminished both in power and range ; there was no change in the reflexes. On the 61st day the left arm began to improve and during the next few days the patient was able to move it well both at the wrist and elbow, but not at the shoulder. The other signs remained unchanged ; the left leg was still very weak but no alteration had occurred in the reflexes.

On the 71st day of illness movement began to return at the

shoulder, and by the 80th day, that is 30 days after the onset of paralysis, the arm had fully recovered. About the same time the left leg, which had remained weak, began to show the characteristic signs of an upper neurone lesion. On the 84th day, four days after normal cerebro-spinal fluid had been obtained for the first time, the left knee jerk was considerably brisker than the right, both patellar and ankle clonus were present on the left side, and the left plantar reflex was definitely extensor ; Oppenheim's reflex was also positive. The patient was unable to raise the leg at the hip but could draw the limb up as he lay in bed. Left drop-foot was pronounced and dorsi-flexion only very feeble. Within six weeks of recovery from meningitis, however, the patient was walking, although with a limp.

The paresis gradually improved, and when the boy was seen six months later, he was still walking with a slight limp but there was no drop-foot, the anterior tibial and peroneal muscles showing good power. No voluntary movement was apparent in the great toe, and the gastrocnemius and soleus muscles were very weak, plantar flexion being extremely feeble ; the other toes he was able to flex and extend slightly. All other muscles were normal. There was neither patellar nor ankle clonus, but the left knee and ankle jerks were still brisker than those on the right, and the plantar reflex remained extensor. The arm was perfectly normal.

Occasionally hemiplegia may develop in severe cases shortly before death ; in one such case Foster and Gaskell found, on post-mortem examination, a massive deposit of pus over the associated Rolandic area. In the case we have described above the primary lesion was probably of a similar nature, organisation occurring later.

H. D. Rolleston mentions a case of cerebro-spinal fever developing hemiplegia, in which softening of the internal capsule was found on post-mortem examination. In one case we met with some time after recovery from a severe attack of the disease, the persistent hemiplegia may have owed its origin to a similar cause ; the paralysis was accompanied by aphasia.

CASE XXXVI.—The patient, aged 25, experienced an acute onset with rigors, headache and vomiting. He was delirious and more or less unconscious for about 14 days ; during this period complete right-sided hemiplegia, together with motor aphasia, had gradually developed. The paralysis was at first flaccid but later became spastic. The patient recovered from meningitis after a course of about four weeks' duration.

Four months after recovery some voluntary movement appeared in the leg ; three months later he was able to walk with the aid of a stick. With re-educative methods the aphasia improved but the arm remained paralysed. When examined by one of us some 12 months after recovery, the condition was as follows :

A considerable degree of motor aphasia—hesitancy, slowness and slurring of speech ; difficulty in forming words and expressing himself.

Paresis of right side of face—upper neurone type.

Arm shows spastic paralysis and is held across the chest with the forearm pronated ; weakness of all shoulder muscles, paralysis of the deltoid, weak movement in the biceps and triceps, but paralysis of all muscles below the elbow.

The right supinator, biceps and triceps jerks are all brisker than those on the left.

The left abdominal reflex is brisk but the right very sluggish. The right leg shows fair voluntary movement at the hip and knee ; there is paralysis of the calf muscles (gastrocnemius, soleus, etc.), and the anterior tibial group possess only very feeble movement. The toes exhibit very slight flexion and extension. The right knee and ankle jerks are considerably brisker than those on the left ; ankle clonus is absent, but the right plantar response is extensor.

A transient hemiplegia, lasting only a day or two, is probably due to local oedema.

In general, the prognosis of hemiplegia occurring during the course of cerebro-spinal fever is good, but when the paresis lasts for some time, residual palsies often remain.

In rare instances an intercurrent cerebral haemorrhage may occur, especially in patients with pre-existing chronic nephritis ; if not fatal, it usually leads to permanent hemiplegia.

Monoplegia and Paralysis of Muscle Groups or of Individual Muscles.—A flaccid paralysis, localised to one limb or even an individual muscle, is occasionally met with. In some cases the condition may be merely transitory and, as recovery proceeds, pass off within a day or two. In other cases, however, the paralysis is more persistent and leads to the disappearance of the deep reflexes and muscular atrophy ; later, on electrical testing, a reaction to degeneration may also be found in the affected muscles. The paralysis, therefore, is typical of a lower neurone lesion. In the following example a flaccid paralysis affected the right arm, together with a more transient paresis of the deltoid muscle in the left arm.

CASE XXXVII.—A subacute case, that of a child aged six years, exhibited on the seventh day of illness considerable weakness of both arms. Three days later the patient was unable to raise either arm at

the shoulder, the deltoid muscles being paresed and flabby ; paralysis of the right biceps and triceps was also present, no degree of active flexion or extension being possible at the elbow. The supinator, biceps and triceps jerks were unobtainable in both limbs, and hyperaesthesia was particularly marked in the right. By the 14th day there was a fair amount of wasting of the affected muscles in the right arm. Meningococci were present in the cerebro-spinal fluid until the ninth day of the disease, and recovery from meningitis, as shown by the evacuation of a clear cerebro-spinal fluid on lumbar puncture, was not complete until the 30th day.

Fourteen days after recovery, movement in the left arm had returned but the right still showed paresis of the deltoid, biceps and triceps. No response to faradism was obtained in these muscles, and with galvanism ACC was greater than KCC in the deltoid ; in the biceps and triceps ACC was equal to KCC. There was also some weakness and wasting of the intrinsic muscles of the right hand in comparison with the corresponding muscles of the opposite limb, and they reacted very sluggishly to faradism.

The following case illustrates a similar condition affecting the lower limb.

CASE XXXVIII.—A child, aged seven years, and recovering from an acute attack of cerebro-spinal fever, showed pronounced weakness of the right leg on the 10th day of illness. On examination, paralysis was found affecting all muscles below the knee, no voluntary movement at the ankle or in the toes being possible. The patient was able feebly to extend and flex the limb both at the knee and the hip. The right knee and ankle jerks were absent, and Kernig's sign was considerably less marked on the affected side. On the 14th day, normal cerebro-spinal fluid was obtained on lumbar puncture for the first time.

Two weeks after recovery right drop-foot was still present, together with paralysis of the gastrocnemius and soleus muscles ; slight extension of the toes was possible but no flexion. The deep reflexes remained absent. At the knee and hip voluntary movement was good. Sensation, as regards response to pin-pricks, appeared deficient over areas corresponding to the distribution of the fourth and fifth lumbar and first and second sacral nerves.

When seen four months later the patient had fair voluntary movement both at the ankle and in the toes ; sensation appeared normal.

Flaccid paralyses, such as the above, are due to the involvement of spinal nerve roots, probably as a result of purulent infiltration of their pia-arachnoid sheaths as they pass out from the spinal cord. Unless the paralysis is very extensive, the prognosis is hopeful as regards ultimate recovery of movement ; occasionally, however, the condition may persist for several months.

A similar flaccid paralysis, affecting one limb, may sometimes occur towards the end of the course in cases proving fatal. The following is an example.

CASE XXXIX.—A case of the progressively purulent type, dying on the 13th day of illness, exhibited, when profoundly delirious about 24 hours before death, a complete flaccid paralysis of the left lower limb. Kernig's sign, previously present, was absent on the affected side, although still obtainable on the right. Both knee jerks were absent and also the left ankle jerk, that on the right being normal. Plantar stimulation elicited a very reduced flexor response.

A definite anterior poliomyelitis, due to an extension of inflammation from the spinal meninges to the ganglionic motor cells of the anterior horn and leading to permanent flaccid paralysis, is exceedingly rare. Prior to the introduction and general adoption of lumbar puncture, which rendered possible the accurate diagnosis of cerebro-spinal fever, reports of such paralyses were no doubt brought about by mistaking for cerebro-spinal fever the " meningeal " type of acute anterior poliomyelitis. Liebermeister and Lebsanft, however, found histological evidence that degeneration of the anterior horn cells does occasionally occur.

Paraplegia.—Paraplegia, occurring during the course of cerebro-spinal fever, is almost invariably of the flaccid variety resembling that seen in acute myelitis. The condition is illustrated by the following case.

CASE XL.—In a severe case, in which more or less delirium with occasional periods of lucidity had been present throughout the course of illness, a complete flaccid paralysis of the lower extremities was observed on the 26th day. At this time the patient was still delirious and quite incoherent when questioned. Some retraction of the head was present, but with the onset of paraplegia Kernig's sign disappeared, only slight rigidity of the hamstring muscles remaining ; all reflexes were absent, both superficial and deep. Incontinence, previously present at frequent intervals, was replaced by retention of urine on the 25th day, that is, the day before the development of paraplegia. The mental condition of the patient did not permit any estimate of the sensory state being made. He became comatose on the evening of the 29th day, incontinence reappeared, and he died without further change on the 31st day. A post-mortem examination was unobtainable.

The case of a child who developed a flaccid paraplegia late in a typical attack of cerebro-spinal fever is mentioned by Sheffield Neave. The paralysis persisted for many weeks after recovery

from meningitis, and at the time of reporting was said slowly to be improving. No sensory changes are mentioned. Sophian also describes the case of a girl, aged 10 years, who showed a flaccid paraplegia, absent reflexes, loss of sensation and paralysis of the bladder.

In the absence of a complete examination for sensory changes, it is difficult to be certain of the exact nature of the flaccid paraplegia. It is probable that some loss of sensation exists, as a pure anterior poliomyelitis with loss of control of the sphincters is rare. In cases exhibiting sensory loss, the lesion responsible for the flaccid paralysis may be either an involvement of the cauda equina, similar to but more extensive than that which produces monoplegia, or a secondary myelitis; the two conditions may be differentiated according to the distribution of anaesthesia, in patients whose mental state admits its reliability. Lumbar puncture as a cause can practically be excluded. We have systematically examined all recovered cases, in whom puncture had been performed on occasions varying in number from four to thirty-six, with a view to ascertaining the presence or otherwise of any sign of a cauda equina lesion; invariably the result was negative, not even the slightest disturbance of cutaneous sensation being demonstrated.

In most cases complicated by the appearance of a flaccid paraplegia, the suddenness of the onset of paralysis suggests a myelogenous origin. Carnegie Dickson, in a large number of cases of cerebrospinal fever examined post-mortem, found extensive softening of the spinal cord but, as far as we are aware, no authentic case of myelitis has been accurately described.

A considerable degree of weakness in the legs and unsteadiness of gait is frequent during the early stage of convalescence, especially when patients first begin to walk. According to Sophian, in a few instances the knee jerks are exaggerated and a true ankle clonus, with extensor plantar reflexes, may also be found. We have frequently seen ataxia, positive Romberg's sign and difficulty in walking; in some cases exaggeration of the tendon reflexes has also been present, but in no case, in the absence of a definite paresis of upper neurone type, were these symptoms associated with either ankle clonus or a true extensor plantar response. The muscular weakness, as a rule, rapidly improves and the unsteadiness of gait gradually disappears.

Peripheral Neuritis.—Pains in the back and legs, associated with muscular weakness, is frequent during early convalescence. Definite

peripheral neuritis, however, leading to sensory changes and loss of deep reflexes, is rare, but may occur quite apart from the flaccid paralyses already described. We have met with two examples, the lower extremities being affected in each case. Both patients, during the later stages of the disease, complained of considerable pain in the legs ; tenderness was also present along the main nerve trunks, especially the posterior tibial. The knee and ankle jerks, previously present, disappeared early in convalescence, and on examination, loss of epicritic sensibility was demonstrated over the feet and extending up each leg to above the knee, together with a smaller area of protopathic loss. The muscles became weak and somewhat wasted, reacting only sluggishly to faradism ; a complete reaction to degeneration, however, never developed. On suitable treatment the condition gradually improved ; in one case the jerks were beginning to return three months after recovery from meningitis and sensation was nearly normal. The second patient, after a similar period, showed normal sensation but no return of the deep reflexes.

In a few cases loss of the tendon reflexes may occur, although no definite neuritis is present ; the loss is probably due to muscular atonicity as the reflexes are soon regained.

Aphasia.—This is a rare complication ; it has occurred in two only of the cases with which we have met. Case IV. (p. 70), that of a girl aged 13 years, on the eleventh day of illness exhibited the following condition : Her general mental condition appeared good and she performed certain actions—protruding the tongue, watching one's finger in testing the ocular movements, etc.—when requested to do so. She was, however, quite unable to speak ; questions were answered in the affirmative or negative by corresponding nods of the head. The condition was accompanied by exaggerated knee and ankle jerks and also a bilateral extensor plantar reflex, but no paresis of either the upper or lower limbs. Two days later (13th day) paralysis of both external rectus muscles of the eye developed. Aphasia was still present, and further, the patient appeared to exhibit agraphia ; when a pencil was placed in her hand and she was told to trace " Yes " or " No " in answer to a particular question, she was quite unable to do so. Nevertheless, she understood clearly all that was said to her. Some incoördination of the upper limbs was also present, as indicated by the test of touching the nose with the tip of the forefinger, the eyes being closed.

By the fifteenth day of illness, the patient's general condition

had much improved and neck rigidity was practically absent. Aphasia with extensor plantar reflexes persisted, but movement in the ocular muscles was returning rapidly. Ten days later (25th day) the patient began to speak, at first in monosyllables only, and also to write imperfectly. Incoördination of the upper limbs had passed off, but the plantar responses remained extensor and did not change to flexor until seven days later. Eventually recovery was complete.

In view of the presence of definite extensor plantar reflexes, the aphasia in the above case was probably due to temporary involvement of the cortical speech centre.

In Case XXXVI. (p. 198) motor aphasia was associated with complete right-sided hemiplegia, including the face.

Cerebral Haemorrhage.—Three cases of cerebral haemorrhage, occurring during the course of cerebro-spinal fever and leading to hemiplegia, are reported by W. J. Denehy. In each case chronic nephritis and degenerative changes in the blood-vessels were found on post-mortem examination. The cerebral congestion brought about by the meningitis was apparently the determining factor in causing vascular rupture.

Small haemorrhagic areas are occasionally met with at autopsy in acute fatal cases.

Cerebral Abscess.—This condition is extremely rare. It may occur secondarily to ulcerative endocarditis or sinusitis. Fairley and Stewart mention one case in which meningococci and B. coli were isolated from the pus. In acute fatal cases, areas of acute encephalitis may be met with at autopsy.

Hydrocephalus.— This important complication is dealt with separately in Chapter IX.

ORGANS OF SPECIAL SENSE

The Eye. (a) *Membranes, Media and Connective Tissues.*

Conjunctivitis.—This condition is more frequent in some epidemics than in others. Of our own cases it occurred in 9 per cent. As a rule, the infection is benign and subsides quickly, but in some cases it may be purulent and lead to one or more of the conditions enumerated below. Meningococci have been isolated from the purulent discharge by Robinson, Neave and others.

Ker and Douglas have reported a case of purulent conjunctivitis,

due to the meningococcus, occurring as a primary infection without any associated meningitis (*vide* p. 353).

Conjunctival haemorrhages may be met with in fulminating and other acute cases ; not infrequently they are followed by conjunctivitis.

Keratitis.—In severe cases superficial corneal ulcers may develop in the absence of other ocular complications of an inflammatory nature ; the ulcers usually heal without perforation.

Simple keratitis was not present in any of our patients but Uhtoff met with the condition in three of 110 cases.

Irido-Choroiditis.—This grave complication is fortunately rare. It has been described as occurring in mild forms of the disease, but usually the cases are of a severe type. Judging from the literature of the subject, irido-choroiditis as a complication of cerebro-spinal fever has appeared less frequently during the last few years than formerly. Although the condition may occur at any stage of the course, as a rule it develops early—within the first four days—and is almost always unilateral, sympathetic ophthalmia being exceedingly rare. Following some conjunctival infection, episcleral oedema develops, being sometimes accompanied by a slight degree of exophthalmos. Purulent exudate appears in the anterior chamber, the media become slightly turbid and a yellowish fundal reflex is obtained. The exudate in organising may cause retinal detachment. Loss of vision is the usual sequel, the eyeball atrophying and the lens becoming opaque. Occasionally, irido-choroiditis may lead to acute panophthalmitis.

Unilateral irido-choroiditis occurred in two of our cases ; both patients recovered from the meningitis but only with considerable impairment of vision in the affected eye. Netter records two cases of suppurative irido-choroiditis, due to the meningococcus, in which the intravitreous injection of anti-meningococcal serum is stated to have led promptly to the abatement of inflammation, sight being retained. A case of double endophthalmitis, developing during the course of an acute attack of cerebro-spinal fever, is recorded by Siredey and Martin.

Netter considers that the position of the patient has considerable influence in determining which eye is affected ; he has noticed that it is the eye of the side on which the patient lies that usually becomes involved.

Panophthalmitis.—This complication is rare but occasionally follows conjunctivitis and irido-choroiditis ; should the case recover

from meningitis, the affected eye usually remains permanently blind. The condition is occasionally unilateral; for instance, Robson and A. L. Pearce Gould report a case, at first showing small conjunctival haemorrhages, which developed bilateral keratitis on the fourth day of illness. This was followed rapidly by acute panophthalmitis, and although the patient recovered from meningitis, complete blindness resulted.

In Fairley and Stewart's series three cases of panophthalmitis occurred; one is said to have recovered with no impairment of vision. Of 410 naval cases, H. D. Rolleston states that panophthalmitis occurred in five; in one case the condition was bilateral.

Orbital Cellulitis is very rare and we have met with no example. Netter and Debré, however, describe a case of double orbital inflammation with bilateral thrombosis of the cavernous sinus.

As regards the mode of production of inflammatory complications affecting the membranes, media, etc., of the eye, the most probable cause is infection *via* the blood stream. Sophian suggests that infection takes place by extension along the pia-arachnoid sheath of the optic nerve; if this were so, however, one would expect to observe irido-choroiditis more frequently than conjunctivitis, which is not the case. Another method of infection that has been suggested is the propagation of meningococcal inflammation from the naso-pharynx along the lachrymal duct.

Vitreous Haemorrhage.—We have not found this complication previously described. It occurred in one of our cases following optic neuritis.

The patient, a subacute case, recovered from meningitis after a course of 30 days' duration. On the 14th day of illness optic neuritis was discovered, the patient complaining of considerable impairment of vision. On the right side neuritis was severe, the disc being completely blurred and the surrounding retina oedematous; the left disc was somewhat blurred in regard to fine details. When examined on the day following that on which clear and normal cerebro-spinal fluid was obtained for the first time (30th day), the right disc was not seen owing to a large vitreous haemorrhage having occurred; the left disc was practically normal. Eighteen days later the right eye was seen to be clearing, but the haemorrhage, obscuring the vitreous, could be identified above the disc. Three months after recovery from meningitis, the patient's vision was as follows: Right Eye, 6/9; Left Eye, 6/6; the vitreous was practically clear.

(b) Nervous Structures.

Optic neuritis and affections of the ocular muscles are dealt with among the symptoms of the disease (p. 123).

Amaurosis.—This is a comparatively rare complication, especially during recent years. It is most frequent in the posterior basic type of the disease affecting infants; according to Langmead, amaurosis develops in 30 per cent of such cases. The condition usually occurs at an advanced stage of illness and is almost always bilateral; in some cases, however, impairment of vision may commence as early as the fourth day, and in a few weeks complete blindness is present. Generally its development is insidious, one of the earliest symptoms in children being a staring and vacant expression. Occasionally sudden amaurosis may occur, which, after a period varying from a few days to several weeks, gradually passes off.

In many chronic cases amaurosis is associated with hydrocephalus; in a few patients the latter condition may bear a causal relationship to the loss of vision. Sophian instances a case in which there was apparent return of vision following the relief of hydrocephalus by direct ventricular puncture. In other cases recorded by Netter and Triboulet and Rolland, the amaurosis, although of central origin, was associated with and appears to have been dependent upon hydrocephalus, vision being regained after repeated lumbar punctures. In such cases the blindness is possibly produced by pressure on the optic tracts.

In the majority of cases of amaurosis, the optic discs show no appreciable change; blanching of the vessels is occasionally observed in hydrocephalic cases, and at a late stage of the condition optic atrophy is not infrequent.

In most cases, the persistent blindness is attributable to permanent changes in the visual centres of the cerebral cortex. The optic centres of the infant, situated immediately beneath the already ossified occipital bone, are easily exposed to greater pressure than are, for example, the motor areas, some degree of separation of the parietal bones being possible at the sagittal suture. Where amaurosis appears somewhat suddenly and after a certain period passes off, it is probably due, in the absence of disc changes, to temporary oedema of the occipital cortex.

Cases other than those of the posterior basic type seldom develop amaurosis; when present, however, it is usually due to optic atrophy, and is permanent and incurable.

The Ear.

Otitis Media.—According to Goeppert, who observed the condition in 35 per cent of cases during the first week, acute catarrhal otitis media is not uncommon. In our own cases it was most infrequent.

Suppurative otitis media, as an immediate result of cerebro-spinal fever, is very rare ; as a direct complication it was not present in any of our cases. Of 450 cases, Fairley and Stewart met with middle-ear suppuration in two patients only ; in one it was associated with a cerebral abscess, meningococci being obtained from the pus.

Chronic otitis media of old standing, with persistent ear discharge, may, of course, be present in patients suffering from cerebro-spinal fever. Such cases may, at first, be regarded as examples of meningitis of otitic origin, especially if organisms are not found on examination of the first sample of cerebro-spinal fluid withdrawn. Otitis media of old standing was present in 7 cases of 160, 6 of whom recovered. In no case were meningococci found in the ear discharge either on direct examination of films or on culture.

When herpes extends from the face into the external auditory meatus, it may give rise to a thin watery ear discharge ; this, however, should easily be recognised.

Deafness of Central Origin.—(a) *Temporary Deafness.*—Deafness occurring at the outset or very early in the course of the disease may show a gradual disappearance as the patient's general condition improves. In some cases the hearing is practically normal by the time or even before the patient has definitely recovered from meningitis ; in most cases of temporary deafness, however, the improvement in hearing occurs during convalescence.

Temporary deafness occurred in four of our patients :

(1) Case admitted in an unconscious state on the third day of illness ; next day the patient was more conscious, but profoundly deaf. On the fifth day deafness was still present, but his mental condition was practically normal. On the seventh day, however, hearing had greatly improved, and by the ninth day it was quite normal. Unfortunately, a recrudescence of meningitis occurred on the 13th day, pneumonia having also supervened on the eighth day, and the patient died on the 16th day of illness.

(2) Case admitted somewhat excited and exhibiting occasional delirium ; the patient was noticed to be very deaf. The deafness, however, gradually improved until, about the tenth day, hearing was normal.

(3) In this case the deafness appeared to be of a mixed type. The

patient, aged 23, was admitted delirious and incoherent within 24 hours of the onset of cerebro-spinal fever. Improvement was fairly rapid, and by the seventh day his mental condition was practically normal, recovery from meningitis being complete on the 14th day of illness. On the eighth day the patient complained of deafness in the right ear ; the tympanic membrane appeared normal, but to Rinné's test both air and bone conduction were markedly diminished. By the 14th day he was deaf in both ears, the right being worse than the left. In the right ear air conduction was absent, but bone conduction fair. On the left side the patient could hear a watch at no greater distance than one inch ; air conduction was better than bone. Within a month of the termination of the 14 days' course of illness, both ears had improved considerably. A month later the left ear was normal and the right only slightly deaf ; on testing the latter, the condition was the reverse of that previously found—air conduction was fair and bone conduction practically nil. The general conclusion is that the deafness on the left side was purely central, while that on the right was mixed, both the nerve and middle ear being affected.

(4) Acute case admitted on the third day of illness, stuporose with occasional delirium. Under the usual treatment the patient progressed satisfactorily, and by the 15th day the cerebro-spinal fluid was quite clear and sterile. No deafness was apparent during the earlier part of the course, but towards the last few days the patient's hearing was noticed to have become markedly impaired. On the ninth day of convalescence, deafness was considerable but not absolute ; in both ears air conduction, though much diminished from normal, was better than bone conduction. There was no evidence of hydrocephalus, and an exploratory lumbar puncture yielded a normal cerebro-spinal fluid under no increased tension. After a further week of comparative deafness, the patient's hearing gradually improved, and about six weeks later (9th week of convalescence) no appreciable abnormality was apparent in the left ear, and in the right there existed only a slight degree of nerve deafness.

The temporary deafness of central origin is probably due to a transient oedema affecting the eighth nerve or the auditory part of the cerebral cortex. In a few cases it may accompany hydrocephalus.

(b) *Permanent Deafness*.—In most epidemics, deafness still remains the most frequent of the more severe complications. Its frequency in cases occurring prior to the introduction of specific serum therapy varied from 12 to 33 per cent, while in 1294 serum-treated cases, analysed by Flexner, permanent deafness occurred in only 3·5 per cent. The cases affected are usually of a severe type, but the condition has been reported as occurring in mild and even abortive cases. The deafness is almost always bilateral and usually

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appears early, rarely later than the first week of illness. Although the patient may improve and finally recover from meningitis, the deafness remains unaltered and is, as a rule, absolute.

In children below the age of seven years, permanent deafness usually leads to an associated mutism; even though speech has begun it gradually disappears. Gassot quotes observations by various writers on the subject of acquired deaf-mutism; according to these, the number of cases in which the condition is attributable to meningitis varies between 8 and 45 per cent: Haberman, for instance, considered that in 100 of 1137 deaf-mutes the disability was due to cerebro-spinal fever.

Permanent deafness was present in four only of our cases, in one of whom it was unilateral.

CASE XLI.—*Permanent Unilateral Deafness.*—The patient, aged 28 years, experienced a sudden onset, consisting of shivering during one evening and vomiting a few hours later; following this, he remembered no more until he arrived in hospital on the third day of illness. On admission he was inclined to be delirious, and exhibited petechiae on the knees and hips, together with the usual signs of meningitis. Lumbar puncture yielded a turbid fluid containing many meningococci.

With repeated daily lumbar puncture and intrathecal serum administration, the patient rapidly improved, consciousness being normal and meningococci absent from the cerebro-spinal fluid after four days (7th day of illness). No deafness was apparent until the 10th day; on the 16th day of illness, when for the first time the cerebro-spinal fluid was quite clear and transparent, the right ear exhibited absolute deafness, neither bone nor air conduction being appreciated; in the left ear hearing was much diminished, but air conduction was greater than bone conduction. The tympanic membranes were normal. The left ear rapidly improved, hearing being normal after the second week of convalescence; the right ear, however, still exhibited absolute deafness three months after recovery from meningitis.

Mode of Production of Permanent Deafness.—The generally accepted view as to the mode of production of permanent deafness is as follows: Purulent exudate extends along the pia-arachnoid sheath of the auditory nerve into the internal auditory canal, resulting in both the 7th and 8th nerves becoming embedded in pus. The relative rarity of marked facial paralysis accompanying deafness is attributed to the fact that the trunk of the 7th nerve, in contrast to that of the 8th, forms a compact bundle of nerve fibres which does not allow the penetration of purulent exudate into its substance. According to some authors, the infiltration spreads along the

aqueduct of the cochlea, and subsequent infection of the perilymph permits its spread into the vestibule and along the terminal filaments of the auditory nerve. As a result of the organisation of exudate, the internal auditory canal becomes filled with cicatricial tissue ; consequently, the trunk and filaments of the auditory nerve degenerate and become atrophied.

In rare instances part of the cochlea and organ of Corti are said to remain unaffected, thus permitting the perception of a certain number of tones.

As long ago as 1881, Moos attributed the deafness occurring in cerebro-spinal fever to thrombosis of the arteries of the auditory nerve, which originate from the middle meningeal artery. This view also serves to explain the comparative rarity of an accompanying facial paralysis, as the arterial supply of the 7th nerve is derived from a different source, viz. the stylo-mastoid artery.

Labyrinthine Disturbances.—Taber, when examining Sophian's cases in the Texas epidemic, 1912, found that in most of those of an acute type, no evidence of labyrinthine involvement could be elicited. In a number of cases exhibiting deafness, however, examined after recovery, there was evidence of considerable involvement of the labyrinth.

Sophian mentions a case running a chronic course, during which deafness occurred ; sudden turning of the head from side to side caused vomiting and nystagmus. Following treatment by lumbar puncture and the relief of hydrocephalus, the hearing improved ; with a return of hydrocephalic symptoms, however, there was a recurrence of deafness and also of the other symptoms mentioned above. The case finally recovered.

Although frequently sought, we have not discovered any definite evidence of labyrinthine disturbances in recovered patients with or without deafness.

In meningitis two types of hydrocephalus are met with :

   (*a*) Generalised Hydrocephalus.

   (*b*) Internal Hydrocephalus.

GENERALISED HYDROCEPHALUS

Generalised hydrocephalus is that type in which an increased amount of cerebro-spinal fluid is present throughout the sub-arachnoid space, both in the ventricles and externally, without obstruction of the foramina of Magendie and Luschka.

In addition to that occurring early in the disease, which has already been considered among the symptoms (*vide* p. 130), general-ised hydrocephalus may develop at any time subsequent to the first week. The characteristic symptoms are practically those of internal hydrocephalus but in a somewhat less severe form—headache, lethargy, vomiting, tremulousness, dilated pupils, etc. ; the tempera-ture usually rises, but may remain at its previous level. On lumbar puncture, however, in marked contrast to internal hydrocephalus, a large quantity of cerebro-spinal fluid under increased pressure is usually evacuated. This affords considerable relief, but it may be necessary to repeat the operation every twelve hours before the hydrocephalus has definitely passed off.

The following case is an example of generalised hydrocephalus commencing on the eleventh day of illness :

CASE XLII. (Fig. 30). — *Generalised Hydrocephalus, occurring during the Course, rapidly relieved by Lumbar Puncture.* — The patient, aged 18 years, was admitted to hospital on the second day of illness. The onset had occurred on the previous day with headache, anorexia, and finally, during the evening, vomiting. In the morning

he was found delirious and sent up to hospital. On arrival, the patient exhibited a condition of stupor interrupted by periods of delirium and incoherency ; he was quite unable to answer questions. Retention of urine was present together with neck rigidity, positive Kernig's sign, and active withdrawal of the leg on plantar stimulation. Lumbar puncture yielded 80 c.c. of turbid fluid containing meningococci.

On the following day there was considerable improvement in the patient's condition, and retention of urine was absent. On each of the first five days in hospital, he was given 30 c.c. of anti-meningococcal serum intrathecally, following which lumbar puncture only was per-

Day of Dis.	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Pulse M		56	80	62	74	76	74	76	80	82	70	80	86	64	64	68
Pulse E		96	60	76	84	72	88	84	92	72	72	76	82	68	68	80
Resp. M		22	20	18	20	18	18	20	20	18	18	20	20	18	18	18	20
Resp. E			16	20	20	16	18	20	20	20	20	18	20	20	20	20
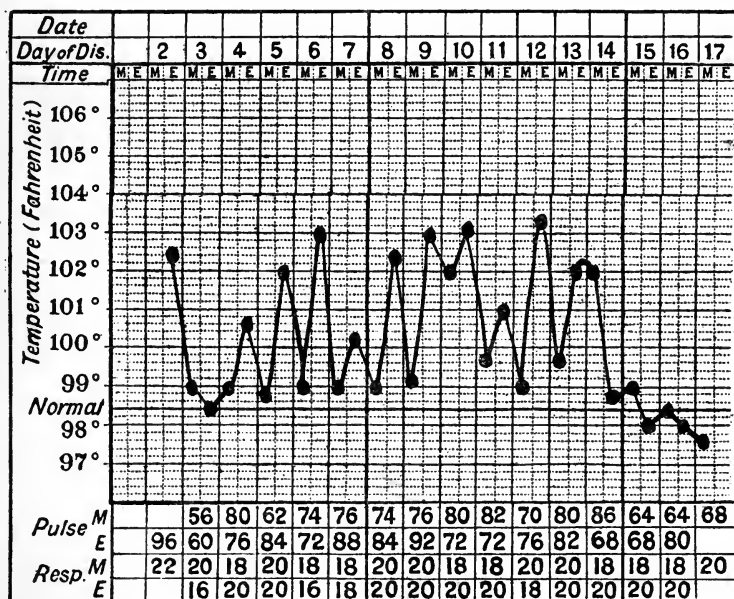
FIG. 30.—Generalised Hydrocephalus, occurring on the 11th day of illness, rapidly relieved by repeated lumbar puncture. (Case XLII. p. 212.)

formed. No meningococci were found in the cerebro-spinal fluid after the fifth day of illness until the ninth day ; consequently serum administration was resumed on the tenth day and continued until the morning of the thirteenth day.

11th Day.—Some vomiting and diarrhoea occurred, and the patient complained of severe headache ; otherwise, there was little change in the general condition. 50 c.c. of slightly turbid fluid were obtained on lumbar puncture, no meningococci being seen or cultivated.

12th Day.—Consciousness, which had been quite normal since the third day, appeared somewhat impaired, and considerable drowsiness was also present. When roused, however, the patient answered questions sensibly. Neck rigidity and retraction of the head also

appeared somewhat more marked. Lumbar puncture yielded 50 c.c. of slightly turbid fluid, in which no meningococci were found.

13th Day.—Drowsiness was more marked, but the lethargy was interrupted by occasional periods of noisy singing. The general signs remained the same, but Macewen's sign was definitely present. Consequently, lumbar was performed both morning and evening, 60-70 c.c. of fluid being obtained on each occasion ; 30 c.c. of serum (the final dose) was given at the earlier puncture only.

14th Day.—The patient's consciousness was quite clear, and the temperature, previously varying from 99° to 103°, had fallen to normal (see Fig. 30) ; it showed no subsequent rises. On lumbar puncture, the cerebro-spinal fluid was found to be only very slightly turbid.

15th Day.—The patient felt quite well, and all symptoms, beyond Kernig's sign and some neck rigidity, were absent. Lumbar puncture revealed a perfectly clear fluid, normal as regards both pressure and microscopical appearance. Following this, convalescence was rapid.

The lumbar punctures, appearance of cerebro-spinal fluid, and doses of serum administered are shown in the following table :

Day of disease.	Amount of c.-sp. fluid obtained on L. puncture.	Appearance of c.-sp. fluid (naked-eye).	Meningococci.	Doses of serum.
2nd	50 c.c.	Turbid	+	30 c.c.
3rd	50 ,,	,,	+	30 ,,
4th	50 ,,	Slightly turbid	+	30 ,,
5th	60 ,,	,,	+	30 ,,
6th	48 ,,	,,	−	30 ,,
7th	40 ,,	,,	−	−
8th	40 ,,	,,	−	−
9th	50 ,,	,,	+ (few)	−
10th	50 ,,	,,	−	30 c.c.
11th	40 ,,	Very slightly turbid	−	30 ,,
12th	50 ,,	,,	−	30 ,,
13th {	40 ,,	,,	−	30 ,,
	60 ,,	,,	−	−
14th	50 ,,	,,	−	−
15th	45 ,,	,,	−	−

In many cases, however, generalised hydrocephalus does not yield to treatment as rapidly as in that described above ; in the following case the hydrocephalus was of somewhat longer duration.

CASE XLIII.—Generalised Hydrocephalus.—The patient, aged 17 years and acutely ill during the earlier stages of the disease, developed generalised hydrocephalus, in spite of repeated daily lumbar puncture, on about the fifteenth day of illness. The amount of cerebro-spinal fluid obtained on puncture was invariably large (40-60 c.c.), and no

meningococci were seen in or cultivated from the fluid after the eighth day. During the three or four days preceding the fifteenth day, the patient's mental condition had been quite normal ; deafness, however, was a marked feature throughout the course.

15th Day.—Occasional delirium was present and the patient vomited. Lumbar puncture : 60 c.c. of turbid yellow fluid under no increased pressure.

16th Day.—Delirium continued. The pupils were somewhat dilated and strabismus was prominent, the left external rectus muscle being paresed. Otherwise the signs were unchanged. L. puncture : 60 c.c. of turbid yellow fluid.

17th Day.—The patient was extremely drowsy with incontinence of faeces and considerable tremulousness. The pupils were widely dilated, and there was a marked tendency to exophthalmos ; paralysis of the left external rectus was complete.

10 A.M. L. puncture : 60 c.c. fluid (turbid yellow).

10 P.M. L. puncture : 70 c.c. fluid (turbid yellow).

18th Day.—Drowsiness, incontinence, and other signs as before. Exophthalmos less.

10 A.M. L. puncture : 60 c.c. fluid (turbid yellow).

10 P.M. L. puncture : 50 c.c. fluid (turbid yellow).

19th Day.—Mental condition improved and the patient spoke rationally ; incontinence of faeces ceased. Exophthalmos absent, and some movement returned to the left external rectus muscle.

10 A.M. L. puncture : 50 c.c. fluid (slightly turbid—yellowish).

10 P.M. L. puncture : 40 c.c. fluid (slightly turbid—yellowish)

20th Day.—Mental condition appeared normal, the patient dictating a letter quite well. Tremulousness was only slight. The pupils were less dilated and the ocular movements normal.

L. puncture : 50 c.c. fluid.

No further signs of hydrocephalus appeared and the patient rapidly improved. Lumbar puncture was continued for three further days, the cerebro-spinal fluid being quite normal on the 23rd day of illness. Deafness, however, which had been present from the onset, persisted.

In chronic cases of cerebro-spinal fever, generalised hydrocephalus is occasionally found to persist even after apparent recovery from meningitis. This result, no doubt, is due to organised exudate and adhesions of the pia-arachnoid diminishing the total capacity of the sub-arachnoid space, and also, possibly, to some extent limiting the absorption of cerebro-spinal fluid. Cases, usually children, may come under observation and, on examination, suggest a condition of hydrocephalus. A history may be obtained of an obscure illness, accompanied by headache and vomiting, some weeks or even months previously, and from which the patient was supposed to have recovered. On lumbar puncture a clear fluid will usually be

obtained; later, the patient may die suddenly from respiratory failure. Such a condition is really a chronic meningitis following an acute attack of cerebro-spinal fever from which the patient merely appears to have recovered; some of the so-called relapsing cases are probably of this nature. Aaser describes the case of a child who, at the age of nine months, had an attack of cerebro-spinal fever, meningococci being found in the cerebro-spinal fluid. The child was severely ill for about four weeks and left hospital after seven weeks. During the following months at home, however, the patient became hydrocephalic, completely blind and helpless. Fourteen months later, he again came under observation on account of paralysis; the muscles of the neck were completely paralysed, those of the arms and legs were atrophic, and the child could neither stand nor sit. A year later he was still unable to assume the erect position. During the following six months lumbar puncture was performed twelve times, over 400 c.c. of cerebro-spinal fluid being removed in all; on several occasions cultures of Gram-negative cocci were obtained on " nasgar," but only if the fluid was first " enriched " by being kept in the thermostat for 48-60 hours before inoculation. The child was mentally deficient and improved only very little under treatment.

" L. S. G." records a case, aged 18, under the care of Fawcett, which proved fatal owing to generalised hydrocephalus nearly a year after supposed recovery from cerebro-spinal fever. The patient, following her discharge from an isolation hospital, continued to suffer from headache and pain in the back of the neck. After a few months she was apparently free from symptoms for a short period; later, however, the headache and cervical pain returned and gradually became more severe. When admitted to hospital a year after the original onset of cerebro-spinal fever, the patient exhibited some neck rigidity, but Kernig's sign was absent. The cerebro-spinal fluid proved normal to microscopical and bacteriological examination. One evening, two weeks later, she suddenly gave a cry and became unconscious; respiration stopped half-an-hour later. Although all expedients failed to stimulate natural respiration, with artificial respiration the heart did not cease to beat until five hours later. At autopsy, some excess of clear cerebro-spinal fluid escaped as the brain was removed; all the ventricles were dilated, the lateral only slightly but the iter and the third and fourth ventricles very considerably. Over the medulla the pia-mater was definitely thickened.

A case of chronic meningitis with hydrocephalus, coming under our observation, is described on p. 442 (Case LXIV.).   Although no definite evidence was obtainable, the condition was suspected to be meningococcal.   The daily intrathecal injection of anti-meningo-coccal serum was followed by complete recovery.

As a rule, generalised hydrocephalus affects both the cranial and spinal portions of the sub-arachnoid space, thus rendering the condition capable of relief by lumbar puncture.   In rare instances, however, in spite of repeated lumbar puncture, death may result from hydrocephalus, generalised as regards the cranial cavity and due to a blockage occurring either at the foramen magnum or high in the spinal canal.   For example, the following case proved fatal owing to the fibrino-purulent exudate producing almost complete obstruction at the upper extremity of the spinal theca, in the region of the foramen magnum.

CASE XLIV. — *Generalised Hydrocephalus of the Cranial Sub-arachnoid Space, due to Obstruction at the Foramen Magnum.*—For a month prior to coming under our observation, the patient, aged 18 years, had been in hospital elsewhere suffering from pyrexia of obscure origin which was apparently ascribed to " rheumatism."   The history given by the patient was that he complained of severe headache and " pain all over."   The only record of his illness obtainable was the temperature chart, which showed an irregularly intermittent pyrexia varying between subnormal and 103° F.—extremely suggestive of cerebro-spinal fever.   The rises of temperature had persisted for 16 days ; following this the pyrexia subsided.   Throughout this period the pulse rate had remained below 96 per minute, varying between this figure and 60.   The patient had then been kept in bed for a further five days (21st day of illness), and was finally discharged from hospital 11 days later (32nd day).

The patient stated that on leaving hospital he still felt far from well.   Two days later he commenced shivering, complained of headache during the afternoon, and vomited in the evening.   He was then sent to hospital, being admitted as a case of influenza.   No improvement in his condition was noticed, however, and two days later (3rd day of " second attack " and 38th day of total illness) he came under our observation.   The temperature was then 101° F., pulse 80, and all the usual signs of meningitis were well marked ; he answered questions well but at times was inclined to " wander."   Lumbar puncture yielded a slightly turbid fluid containing meningococci.

Daily lumbar puncture and serum administration were instituted, fair quantities (40-60 c.c.) of cerebro-spinal fluid being obtained ; the colour of the latter, however, tended to become of an increasingly deep yellow.   For the first two days little or no change occurred in

the patient's general condition. His subsequent progress was as follows :

6th Day (41st day of total illness).—The patient became increasingly delirious and exhibited incontinence of urine. On being roused, however, he spoke fairly rationally, stating that he had absolutely no headache. As he was inclined to be tremulous, hydrocephalus was feared to be developing ; lumbar puncture was therefore performed both morning and evening.

11 A.M. L. puncture : 60 c.c. Slightly turbid yellowish fluid.
11 P.M. L. puncture : 60 c.c. Slightly turbid yellowish fluid.
(No increased pressure was apparent.)

7th Day (42nd day of total illness).—Delirium persisted but incontinence was absent. Occasional floccitation was present. Profuse perspiration was a marked feature, being so intense as to necessitate changing the bed-clothes several times. The pupils were dilated and the arms tremulous.

11 A.M. L. puncture : 60 c.c. Slightly turbid yellowish fluid.
11 P.M. L. puncture : 40 c.c. Slightly turbid yellowish fluid.
The fluid trickled only very slowly through the needle ; on each occasion the needle was withdrawn and re-inserted in a different interspace with no better result. 30 c.c. of anti-meningococcal serum were administered at the morning puncture.

8th Day (43rd day of total illness).—Delirium increased and incontinence again made its appearance. No perspiration occurred, but the pupils were very dilated and tremulousness was pronounced. Definite strabismus was observed.

10 A.M. L. puncture : 10 c.c. Deep yellow fluid.
10 P.M. L. puncture : 5 c.c. Deep yellow fluid.
On each occasion the fluid was obtained only with difficulty ; several interspaces were entered, the flow being very slow.

9th Day (44th day of total illness).—The patient died somewhat suddenly during the early hours of the morning.

Autopsy.—The dura mater was found tense, and on incising it a large quantity of slightly turbid fluid escaped. Over the convexity of the cerebrum there was practically no meningitis. At the base, however, tough fibrino-purulent exudate was found over the pons, medulla, and cerebellum, extending as far forwards as the optic chiasma. The exudate also extended downwards to the cervical region of the spinal cord, the spinal canal at the foramen magnum being almost completely occluded. The lateral ventricles were only moderately distended with slightly turbid fluid.

Occasionally, adhesions between the parietal and visceral arachnoid of the spinal cord may bring about a generalised hydrocephalus similar to that described above. In a case mentioned by Foster and Gaskell death resulted from this cause.

INTERNAL HYDROCEPHALUS

Under normal conditions, the cerebro-spinal fluid secreted by the choroid plexus into the lateral ventricles passes from there into the fourth ventricle and thence to the sub-arachnoid space through the median foramen of Magendie and the two lateral foramina of Key and Retzius or Luschka.

According to Merkel, the lateral ventricles also communicate with the sub-arachnoid space at the apices of their descending horns.

When, owing to inflammatory changes, complete or partial occlusion of the foramina of Magendie and Luschka occurs, the cerebro-spinal fluid, being unable to escape through its usual channels, accumulates in excess throughout the ventricular system. Consequently, since normal absorption is only possible from the sub-arachnoid space, a condition of dilatation of the ventricles results.

Internal hydrocephalus is usually accompanied by posterior basic meningitis, not only in infants but also in other cases. The thick plastering of fibrino-purulent exudate over the pons, medulla and posterior surface of the cerebellum may itself produce some definite obstruction of the foramina ; this is one reason, among others, why internal hydrocephalus is frequent in the posterior basic type of the disease occurring in infants. As the tension in the ventricles rises, their distension causes the cerebral hemispheres to increase in bulk ; on this account all exudate over the vertex is driven into the basal cisternae, thus adding to that already there. In extreme cases, the brain substance becomes considerably thinned and the convolutions flattened by pressure against the cranial walls.

A condition of internal hydrocephalus may further be aggravated by the fact that owing to the increased bulk of the cerebral hemispheres, the cerebellum becomes pressed down against the medulla, thus tending to assist in the obliteration of the foramen of Magendie. On account of the observation that in the recumbent position the posterior horns of the lateral ventricles are the lowest parts of the ventricular system, and, post-mortem, often show the maximum amount of dilatation, it has been suggested that their weight when dilated aids in pressing down the cerebellum upon the medulla. The influence of this factor, however, must be very small since patients developing internal hydrocephalus seldom remain in a supine position but usually lie on the side.

It is rare for both the foramen of Magendie and foramina of Luschka to become completely obstructed. The former is not infrequently occluded as the result of inflammatory adhesions between the cerebellum and medulla ; when this occurs, the natural outlets of the fourth ventricle (foramina of Luschka) may undergo a compensatory dilatation. On account of the protection afforded by the cerebellar peduncles to these lateral foramina, their complete obliteration is very rare and occurs only when the arachnoid is greatly thickened as, for instance, in very chronic cases. Organisation of the basal exudate may also produce permanent blockage by the formation of fibrous adhesions between the structures at the base of the brain.

Internal hydrocephalus is not invariably due to the mechanical closure of the foramina of Magendie and Luschka. It may arise, even in posterior basic types, without occlusion of these orifices, owing to the lack of mechanical resistance offered by the ventricular walls to the total increase of fluid and internal pressure. The softening of the tissue surrounding the ventricles by oedema and often by actual inflammation facilitates such a procedure to a considerable extent. This factor, however, is probably of greater importance in patients where hydrocephalus occurs comparatively early in the course rather than in chronic cases.

Experiments performed post-mortem serve to illustrate the obstruction of the ventricular outlets that occurs in internal hydrocephalus. After the removal of some cerebro-spinal fluid from the lateral ventricle through a trephine hole, an equivalent quantity of methylene blue is injected ; about half-an-hour later the skull is opened and the base of the brain examined. Since some absorption of cerebro-spinal fluid tends to take place post-mortem, in comparing results, the autopsy should be performed on each case at a constant interval after death. By this means it is found that in cases uncomplicated by internal hydrocephalus, the methylene blue reaches the posterior fossa in large quantities. When, however, internal hydrocephalus is present, a very small amount only is usually found outside the ventricles ; occasionally, it is discovered in larger quantity on one side than on the other, suggesting that one foramen of Luschka is more patent. When the obliteration of the outlets is complete, no methylene blue is visible in the posterior fossa ; this, however, is very rare.

Dandy and Blackpan have shown clinically that phenolsulphonaphthalein, when injected intraventricularly, is excreted in

the urine in small amounts only where internal hydrocephalus exists.   Experimentally, the same observers have produced internal hydrocephalus by (1) the mechanical blockage of the aqueduct of Sylvius, and (2) low ligation of the vena Galeni magna ; high ligation had no such effect.   Clinically, therefore, it is possible for either blockage of the Sylvian aqueduct by purulent exudate or thrombosis of the vena Galeni to produce internal hydrocephalus ; as far as we are aware, however, the latter condition, originally suggested by Carr in 1897, has not been demonstrated at autopsy, but Foster and Gaskell mention one case exhibiting, on post-mortem examination, well-marked hydrocephalus of the lateral and third ventricles, the iter being completely blocked.

Time of Appearance, etc.—Internal hydrocephalus may occasionally occur at a comparatively early stage of the disease, but usually it appears as a late complication, developing in cases that have become subacute or chronic.   The onset is sometimes quite sudden but is far more frequently insidious.   A sudden onset is most often met with when internal hydrocephalus occurs early in the course, that is, within the first two weeks of illness ; the explanation of this may lie in the fact that at this stage of the disease, purulent exudate is more general than later, and free flakes of pus may cause a sudden blockage of one or more of the foramina leading from the ventricular system.

Excepting in the posterior basic type of the disease in infants, cases showing marked head retraction do not apparently exhibit any greater tendency to develop internal hydrocephalus.

Symptoms of Internal Hydrocephalus.—Headache is usually one of the first symptoms ; it is, however, variable, and we have seen cases in which it has apparently been absent.

The mental condition may at first be practically normal, but the patient soon becomes drowsy and lethargic although he may still answer questions rationally if roused.   With increasing lethargy loss of memory for recent events may occur (*vide* p. 105), recollection of past experiences remaining clear.   Periods of low muttering delirium are frequent.   Children show a progressive loss of interest in their surroundings, lying quietly for hours with a peculiarly vacant look.   Towards death, a comatose condition is almost invariable. French authors mention a hydrocephalic cry (*crie hydrocéphalique*)— purposeless and of high-pitched, anxious tone—which is quite automatic and independent of pain.   It is encountered only in extreme hydrocephalus.

In most cases incontinence of faeces, with retention or incontinence of urine, is present.

Progressive wasting occurs, in spite of the ingestion of considerable quantities of food, until in advanced cases the emaciation may become extreme. The wasting is probably trophic in origin (*vide* p. 130). In addition, the skin becomes dry and scaly, and bedsores are liable to occur.

In infants, the anterior fontanelle may be found tense and bulging, and not infrequently some separation of the cranial sutures occurs, together with dilatation of the superficial veins of the scalp. Consequently, the head may actually become enlarged, the soft brain tissue and skull cap with its open fontanelles and loosely united sutures offering no great resistance to the accumulation of fluid within the ventricles. In older children, Macewen's sign (p. 132) can almost always be elicited, but in adults, owing to the thickness of the skull, it is somewhat uncertain. In some adolescents, however, we have succeeded in demonstrating the sign.

Persistent vomiting is a frequent feature. It is " cerebral " in character, appearing at irregular intervals and bearing no relation to the taking of food.

The patient becomes progressively more tremulous, intention tremor being particularly well marked. Muscular twitchings also are very frequently observed. Convulsive seizures may occur especially in children, but in adults they are by no means rare ; the seizures consist of generalised clonic movements or of tonic spasms interrupted by clonus.

The degree of pyrexia depends upon the stage of illness at which the complicating hydrocephalus appears ; usually it is ordinarily associated with subacute or chronic types of the disease (*vide* Course, p. 172). In many cases, especially when internal hydrocephalus develops late in the disease, the temperature remains normal or even subnormal.

On account of the increase in intracranial pressure, one might suppose that the pulse rate would be comparatively slow. By no means, however, is this the general rule ; in the majority of cases we have found a persistently weak and rapid pulse. In generalised hydrocephalus of short duration, the pulse rate usually remains slow.

The respiration may show any of the variations already described among the symptoms of the disease (p. 92). In most cases the immediate cause of death is respiratory failure. When this occurs,

the patient becomes cyanosed and rigid and the respiration ceases, but the pulse may continue for several minutes. Gaskell found that hydrocephalic patients could be kept alive for some time by means of artificial respiration.

The general signs of meningitis, *e.g.* neck rigidity, Kernig's sign, are usually pronounced ; in fact, the muscular rigidity often becomes more intense with the development of hydrocephalus. In a few cases neck rigidity may not be apparent, but Kernig's sign has a tendency to persist. Retraction of the abdomen is occasionally observed.

General hyperaesthesia is frequently present, and the vaso-motor system, as indicated by transient erythema, flushing, etc., shows considerable instability.

Marked dilatation of the pupils with a sluggish reaction to light is almost invariable. Ocular palsies are also frequent, the external rectus muscles most often being affected. A certain degree of exophthalmos is sometimes apparent even in adults ; in children the eyes may be turned downwards with considerable retraction of the upper lids. Lateral nystagmus is a frequent sign ; of 19 cases developing internal hydrocephalus, Fairley and Stewart found nystagmus in 14. Optic neuritis, in contrast to other conditions associated with increased intracranial pressure, is rarely seen ; if present, it is usually observed only at the beginning of hydrocephalus and soon disappears. According to Harvey Cushing, the optic neuritis of intracranial disease is the result of increased pressure in the vaginal sheath of the optic nerve ; this, in turn, is produced by the total increase of pressure in the general subarachnoid space forcing the cerebro-spinal fluid into the nerve sheaths. If this view be correct, the absence of optic neuritis in internal hydrocephalus would be accounted for by the fact that there is little or no fluid in the subarachnoid space to be forced into the vaginal sheaths. Any fluid remaining after the occlusion of the ventricular outlets is usually removed by lumbar puncture ; at first, there may be some residual fluid, a fact that would explain the disc changes occasion-ally observed early in the complication.

Blindness of central origin may occasionally develop. It is most often seen in infants suffering from the posterior basic type of the disease. According to Heiman and Feldstein, one-third of such cases show amblyopia.

Facial paralysis is an occasional symptom.

Permanent deafness may sometimes result ; it is no more

frequent, however, in internal hydrocephalus than in the ordinary form of cerebro-spinal fever.

The tongue is unusually dry and tremulous, but paralysis of the hypoglossal nerve is very rare.

The deep reflexes may be sluggish but we have found them more frequently brisk or somewhat exaggerated. Ankle clonus can sometimes be elicited. An extensor plantar reflex is said occasionally to be obtained but in our experience is rare. The abdominal reflexes are usually absent.

The cerebro-spinal fluid obtained on daily lumbar puncture steadily diminishes in quantity until often none can be withdrawn. Such a " dry puncture," however, is only authentic after three or more different intervertebral spaces have been penetrated with negative results. If one interspace only had been entered, one is not justified in regarding the evacuation of cerebro-spinal fluid impossible (*vide* Lumbar Puncture, p. 414). The amount of fluid obtained on lumbar puncture naturally depends upon the quantity remaining in the subarachnoid space; this in turn is dependent upon the relativeness or absoluteness of the block occurring at the foramina of Magendie and Luschka. If the occlusion is only partial, some cerebro-spinal fluid, though small in amount, will be obtained ; if obstruction is complete, the canal will appear dry. In old-standing cases the fluid in the ventricles tends to become clear and sterile, and occasionally may become secondarily infected with other organisms, *e.g.* the pneumococcus.

Diagnosis of Hydrocephalus.—The appearance of increasingly severe headache and lethargy, together with vomiting, tremulousness, dilated pupils, and possibly nystagmus, should lead one to recognise developing hydrocephalus. The importance of its early recognition cannot be sufficiently insisted upon, as speedy and repeated lumbar puncture may avert a threatening internal hydrocephalus (*vide* Chapter XVIII. p. 448). The distinction between generalised hydrocephalus occurring late in the disease and internal hydrocephalus can only be made with certainty upon lumbar puncture ; in the latter case, either no fluid is obtainable or else only a small quantity is withdrawn even on repeated puncture. If blockage occurs in the region of the foramen magnum, as in Case XLIV. (p. 217), differentiation by lumbar puncture will be impossible.

The following example illustrates internal hydrocephalus developing in an adult case which terminated fatally on the 54th day of illness :

CASE XLV. (Fig. 31). —The case occurred during 1915 when the anti-meningococcal serum available was not yielding satisfactory results. At the time, treatment by lumbar puncture alone was relied upon, but we had not then adopted the practice of routine daily puncture, repeated until normal cerebro-spinal fluid is obtained, which will be described later (p. 405, Treatment). Under the latter treatment, no similar case in an adult has occurred in our series.

The patient, aged 25, was a subacute case of the disease, and had been regarded elsewhere, prior to admission, as suffering from influenza. Consequently, it was not until the 13th day of illness that he came under our observation. On admission consciousness was normal, neck rigidity moderate, and Kernig's sign present but not well marked. The temperature was 100° F., pulse 110, and general hyperaesthesia was pronounced.

From the 14th until the 34th day of illness the patient's general condition showed very little change; periods of delirium, usually nocturnal, were frequent, together with occasional incontinence. The temperature seldom rose above 100° and was often subnormal; the pulse rate varied between 80 and 120
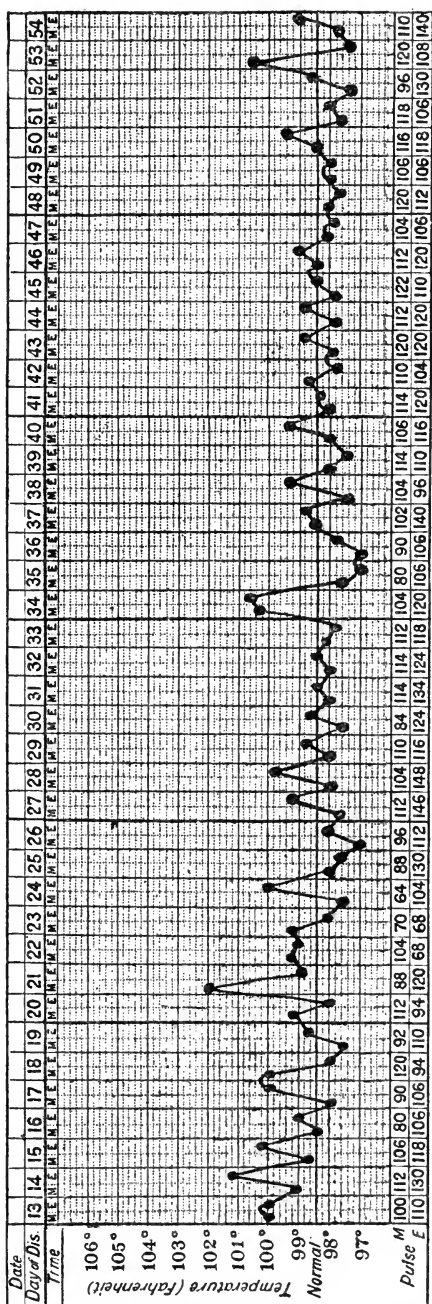
FIG. 31.—Internal Hydrocephalus. Subacute case developing Internal Hydrocephalus with a fatal result. (Case XLV. p. 225.)

per minute. After the first few days, lumbar puncture was performed at intervals of two or three days—treatment which later experiences have shown to be wholly unsatisfactory. A few meningococci were seen from time to time in stained films of the centrifugalised deposit, but their appearance was by no means constant; in culture no growth was obtained after the 22nd day. On the 34th day of illness the patient had a peculiar trembling attack, lasting about one hour and unassociated with any rise in temperature; following this, gradually increasing drowsiness made its appearance. From this time the signs of internal hydrocephalus rapidly developed. Progressive emaciation took place, reaching an extreme degree by the end of the course; the patient became increasingly tremulous and lethargic, frequently lying with open mouth and semi-closed eyelids. Incontinence of both urine and faeces persisted. The pupils were dilated and the spine and limbs rigid, the latter invariably being maintained in the position of flexion. On the 37th day vomiting ensued and continued, occurring almost daily; lumbar puncture gave no relief.

During the last few days of illness, the patient was unable to swallow and lay apparently stuporose, yet occasionally calling out incoherently. The corneae were dry and the sclerotics congested; divergent strabismus was now present. Also, the pulse had increased in rate (100-120), the head was retracted, and the spine rigid, with a marked tendency to opisthotonus. Finally, on the 54th day, a generalised convulsive seizure occurred, the patient dying in coma about four hours later.

Until about the 48th day cerebro-spinal fluid was obtained in varying quantities whenever lumbar puncture was performed. From this time onwards, however, the amount obtained rapidly diminished, the rate of flow becoming extremely slow. On the 52nd and 53rd days only 5 c.c. and a few drops respectively could be withdrawn, although several intervertebral spaces were entered. On the day of death no fluid whatever was obtainable.

Autopsy.—The dura mater was tense, but on opening the membrane no fluid escaped. The cerebral convolutions were markedly flattened, no meningitis was visible over the vertex or lateral aspects of the cerebrum, and no sinus thrombosis was present. Well-marked meningitis, apparently of some standing, was found involving the posterior basic region; fibrino-purulent exudate extended over the pons, medulla, and under the surface of the cerebellum. The meninges about the pons showed considerable opacity and thickening.

The brain tissue was somewhat soft and oedematous, and the ventricles were greatly distended with slightly turbid fluid; the posterior horns, in addition, contained a little pus.

Most authorities consider that internal hydrocephalus, once definitely established, is invariably fatal. When the occlusion of the ventricular outlets is complete and permanent, death of course would be the only possible termination. Naturally, a diagnosis of

internal hydrocephalus is always open to suspicion in cases recovering, as the condition is not confirmed by autopsy. Nevertheless, a case may present all the typical signs of internal hydrocephalus, including " dry punctures," and yet recover. Post-mortem, as already mentioned, complete obliteration of the foramina is rarely found. It is fair to assume, therefore, that in the majority of cases of internal hydrocephalus, the interference with the outlets stops just short of complete occlusion. Early recognition of hydrocephalic symptoms and treatment by repeated lumbar puncture may often prevent the hydrocephalus from becoming entirely internal. As Foster and Gaskell point out, the effect of the punctures may gradually lessen the maximum tension below a certain critical point at which normal drainage is able to take place. Following a period of serum administration, treatment by repeated daily lumbar puncture until normal fluid is obtained tends to avert the development of internal hydrocephalus (vide p. 427). When, however, the amount of cerebro-spinal fluid obtained progressively diminishes and reaches the stage of " dry punctures," other methods of treatment have to be considered (vide Chapter XVIII. p. 449).

The following case illustrates a patient presenting the typical picture of internal hydrocephalus and recovering :

CASE XLVI. (Fig. 32).—A soldier, aged 23, was admitted to hospital in a stuporose condition on the second day of illness, the onset of the disease having occurred suddenly on the previous day. A petechial rash was present over the extensor surfaces of the limbs and also to a slighter extent on the trunk. Neck rigidity, Kernig's sign, and incontinence of urine were also present. Lumbar puncture yielded 55 c.c. of turbid fluid under increased pressure, and which was subsequently found to contain numerous meningococci.

During the first week of illness, the patient's mental condition improved to a certain extent ; at times he would answer questions sensibly and at others relapse into incoherent delirium. Herpes appeared on the fourth day and became very extensive, involving the circumoral region, chin, nose, and both cheeks. Incontinence of urine and faeces was usually present and the general muscular rigidity remained unchanged. Towards the end of the second week the patient showed some improvement ; he was less restless, incontinence was not so frequent, and his consciousness appeared clearer. Gradual and progressive wasting had, however, occurred.

From the day of admission (2nd) until the 14th day of illness, the daily lumbar puncture had yielded fair though somewhat variable quantities of cerebro-spinal fluid ; the amounts ranged between 12 and 75 c.c. per puncture. In appearance the fluid was usually yellowish
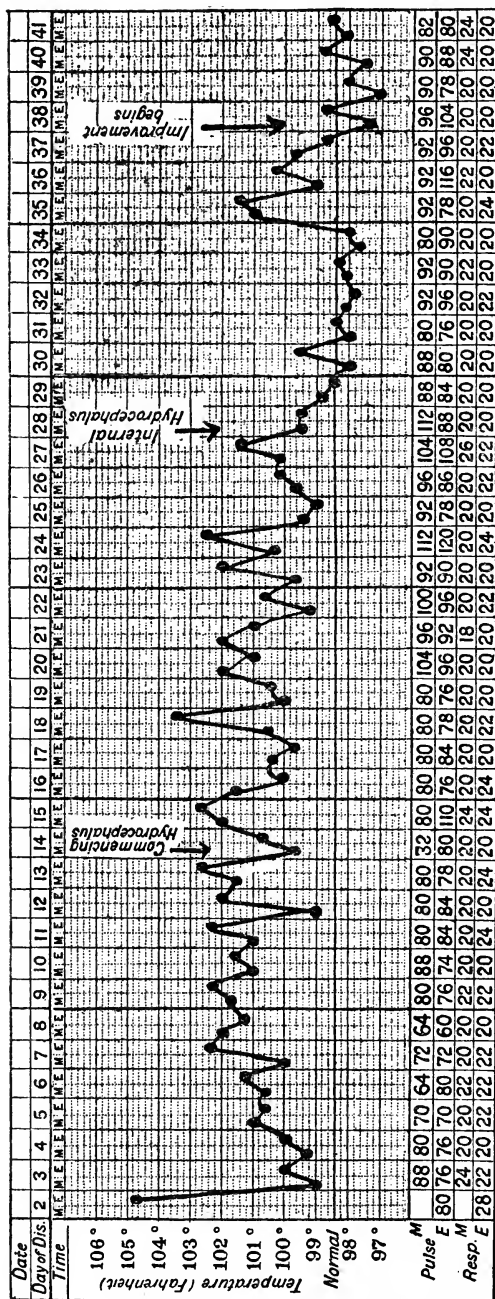
Fig. 32.—Internal Hydrocephalus, terminating in recovery. (Case XLVI. p. 227.)

and always turbid; meningococci were frequently present and proved in culture to be Type I. (Gordon) organisms. From the 15th to the 26th day lumbar puncture gave very variable results. Frequently no cerebro-spinal fluid could be obtained in spite of the penetration of several intervertebral spaces as high as that between the first and second lumbar vertebrae; at other times several c.cms. of fluid would trickle slowly through the needle. The symptoms during this period consisted of occasional delirium and restlessness associated with intervals of apparently normal consciousness. The patient became progressively emaciated, and incontinence of urine and faeces was present practically throughout.

After the 27th day the patient became very drowsy and lethargic; emaciation became more marked and was associated with increasing tremulousness and fre-

quent vomiting. Incontinence continued and general hyperaesthesia was pronounced. The pupils were widely dilated, the deep reflexes exaggerated, and ankle clonus was occasionally elicited. No fluid could be obtained on lumbar puncture in spite of piercing the theca as high as the interspace between the 10th and 11th thoracic vertebrae. During this period the treatment consisted only of vaccine.

The symptoms in relation to lumbar punctures, serum administration, etc., are illustrated in the table on the following page.

By the 43rd day of illness no neck rigidity was apparent, but incontinence of urine did not disappear completely until three days later. The patient remained in a very weak condition for some weeks, but nevertheless gradual and steady improvement took place. Kernig's sign was not definitely absent for nearly six weeks after all other signs had disappeared, and tremulousness was of even longer duration.

When last seen, five months after recovery, the patient showed well-marked symptoms and signs of neurasthenia—rapid fatigue on exertion, pupils somewhat dilated, tendon reflexes exaggerated, tremors of the outstretched hands, and free perspiration. His mental condition, however, was quite normal, and there was no evidence of organic nerve disease.

Three cases of cerebro-spinal fever who developed apparent internal hydrocephalus, eventually recovering after long courses, are also mentioned by Fairley and Stewart. When recovery takes place in such cases it is often complete ; permanent mental impairment, however, may occur in children (*vide* Sequelae, p. 475).

The Morbid Anatomy of Hydrocephalus is further considered in Chapter XV.

Day of Disease.	Amount of C.-sp. Fluid obtained on Lumbar Puncture.	Appearance of C.-sp. Fluid.	Meningo-cocci (Direct Exam.).	Doses of Serum.	Vaccine (Poly-valent).	Symptoms.
				c.cm.	mill.	
2nd	55 c.cm.	Turbid	+	30	—	
3rd	A.M. 30 ,,	Very turbid	+	30	250	
,,	P.M. 15 ,,	,,	+	25	—	Towards the end of the week the patient's mental condition improved to some extent. Incontinence, however, was usually present.
4th	12 ,,	,,	+	20	—	
5th	35 ,,	Blood-stained	+ (Diminished number)	30	—	
6th	30 ,,	,,	+	30	500	
7th	25 ,,	Orange turbid	—	30	—	
8th	12 ,,	Dk. yellow (turbid)	—	—	—	
9th	35 ,,	Sl. blood-stained	—	30	—	Slight improvement, less restless, mental condition clearer, and incontinence occasionally absent.
10th	75 ,,	Yellow (turbid)	—	30	1000	
11th	60 ,,	,,	—	—	—	
12th	75 ,,	,,	+ (few)	—	—	Periods of delirium alternating with normal consciousness.
13th	55 ,,	Yellowish (turbid)	+	30	—	
14th	Nil ; three interspaces entered	..	..	..	1500	Muscular rigidity more marked.
15th	5 c.cm.	Blood-stained	—	—	—	Mental condition worse. Singing or talking incoherent nonsense.
16th	5 ,,	,,	—	20	—	Pupils dilated. Restless, severe headache, occasional delirium.
17th	Nil ; three interspaces entered	..	..	..	—	,, ,,
18th	10 c.cm.	Blood-stained	—	25	2000	Mental condition slightly better.
19th	Nil ; four interspaces entered	..	..	..	—	
20th	5 c.cm.	Blood-stained	—	—	—	Mental condition improved, less muscular rigidity.
21st	Nil	..	..	..	—	
22nd	45 c.cm. No fluid obtained from between 2nd and 3rd lumbar, but from between 1st and 2nd lumbar	Slightly turbid	+ (Very few ; no growth)	—	2000	Delirious with occasional hallucinations.
23rd	85 c.cm. From between 1st and 2nd lumbar	,,	+	30	—	Occasional delirium. Incontinent.
24th	10 c.cm.	,,	—	—	—	,, ,,
25th	2 ,,	,,	—	—	—	Emaciation marked.
26th	40 ,, From between 11th and 12th thoracic	,,	—	—	2000	Increased delirium. Incontinent, trophic sores, widely dilated pupils.
27th	30 c.cm. (11th and 12th thoracic)	,,	—	30	—	Deep reflexes exaggerated. Abdominal reflexes absent.
28th	Nil ; several spaces entered up to 11th and 12th thoracic	..	..	..	—	Vomiting, lethargic. Increased muscular rigidity, hyperaesthesia.
29th	No c.-sp. fluid obtainable although the interspaces as high as 10th thoracic vtba. were entered from time to time	..	..	..	—	During this period the patient was lethargic, vomiting from time to time, incontinent and very tremulous.
30th		..	..	..	2000	
31st		..	..	..	—	
32nd		..	..	..	—	
33rd		..	..	..	—	
34th		..	..	..	—	
35th		..	..	..	2000	
36th		..	..	..	—	
37th		..	..	..	—	Pupils were widely dilated and hyperaesthesia was pronounced.
38th		..	..	..	—	
39th		..	..	..	2500	
40th	..	..	..	..	—	Began to improve, takes more interest in surroundings.
43rd	..	..	..	..	..	Mental condition normal.

CHAPTER X

THE CEREBRO-SPINAL FLUID

Physiology.—Normal cerebro-spinal fluid is a clear colourless liquid with a specific gravity of 1007-1008, and yielding a faintly alkaline reaction. Its solid constituents amount to about one per cent of the total fluid and consist mainly of inorganic salts ; of these, sodium chloride is the chief, but small amounts of potassium chloride, magnesium phosphate, and calcium phosphate are also present, together with a trace of iron and sulphates. The fluid contains a small amount of protein, about 0·1 per cent, consisting of albumoses, globulin, and a trace of peptone. The globulin normally present, however, is insufficient to give a definite precipitate with the usual test for this substance, such as the Nonne-Apelt and the Ross-Jones tests.

A reducing substance is also present, the exact nature of which was for some time uncertain ; it has now been definitely shown to be glucose and is easily demonstrated by means of Fehling's test. Finally, the fluid also contains a trace of nitrogenous extractive.

Under pathological conditions the protein content is largely increased, and, according to Halliburton, substances such as cholesterol and a choline-like substance may appear.

The normal cellular constituents of the cerebro-spinal fluid are very scanty, consisting of small lymphocytes (1-7 per cubic millimetre) and an occasional endothelial cell. Polymorphonuclear cells are normally absent.

The Circulation of the Cerebro-spinal Fluid.—Cerebro-spinal fluid is present throughout the subarachnoid space and also in the cerebral ventricular system ; the latter communicates with the subarachnoid space by means of the median foramen of Magendie and the two lateral foramina of Luschka (*vide* Chapter IX. p. 219).

The results of recent research, especially by Dandy, Blackpan, Dixon, and Halliburton, point to the fact that the cerebro-spinal fluid is primarily secreted by the cells of the choroid plexus into the lateral ventricles ; the choroid plexus, therefore, as suggested by Mott, might appropriately be termed the choroid gland. The cerebro-spinal fluid is thus being continually formed and is eventually reabsorbed into the blood stream. Formerly it was thought that its exit from the subarachnoid space was by means of the lymph channels surrounding the spinal and cranial nerves. Dixon and Halliburton, however, found that large quantities of physiological salt solution, to which is added some substance easily recognised by its colour, chemical nature, or physiological action, disappeared within a few minutes of its introduction into the subarachnoid space ; using such methods it was found that the exit is by the blood stream. Substances readily diffusible, *e.g.* adrenaline, nicotine, and atropine, appear in the blood with remarkable rapidity, especially if introduced into the subcerebellar region, and produce their typical physiological actions almost as rapidly as when introduced into the blood stream, that is, within a few seconds ; further, such substances can be almost immediately recovered from the cerebral sinuses.

Dandy and Blackpan, by means of phenolsulphonaphthalein injections into the subarachnoid space and subsequent urinary examinations, found that absorption was fairly regular for 3-4 hours, and that probably the cerebro-spinal fluid was completely absorbed and renewed every 4-6 hours.

That the process of absorption of cerebro-spinal fluid into the blood stream is purely one of diffusion is shown by the fact that substances not readily diffusible (*e.g.* commercial peptone) do not produce their characteristic effects when introduced into the subarachnoid space ; consequently, the old theory that actual valved orifices exist leading into the larger cerebral veins is untenable.

Diffusion probably occurs into the venous sinuses by means of the microscopic villi described by Weed, and possibly, in addition, through the thin-walled blood vessels within the central nervous system ; as Mott has pointed out, contact between the cerebro-spinal fluid and these vessels is maintained throughout their course by means of the perivascular spaces which are continuous with the subarachnoid cavity.

The structure of the Pacchionian bodies renders it probable that

they also are concerned in the absorption of cerebro-spinal fluid into the venous circulation.

Diffusion in the opposite direction, that is, from blood to cerebro-spinal fluid, does not occur except in an almost negligible degree in the case of a few drugs, *e.g.* alcohol and urethane.

Between the cerebro-spinal fluid and other parts of the body another minor communication also exists. In 1905 André demonstrated in the dog and rabbit downward prolongations of the sub-arachnoid space accompanying and forming a network around the olfactory filaments as they pass through the cribriform plate to the nasal fossae. More recently these observations have been confirmed by Dixon and Halliburton by adding dyes to the cerebro-spinal fluid and tracing their course. No dye was ever detected in the sheaths of the spinal nerves outside the spinal canal, nor was it discernible in the thoracic duct.

Sicard, in 1900, showed by means of ink injections that the cerebro-spinal fluid also circulates throughout the subarachnoid space itself.

The circulation of the cerebro-spinal fluid, therefore, consists in secretion of the fluid by the choroid plexus into the lateral ventricles ; from here, by means of the Sylvian aqueduct, fourth ventricle and foramina of Magendie and Luschka, it passes into the subarachnoid space, to be reabsorbed into the blood stream by direct diffusion into the vessels throughout the extent of the subarachnoid space.

THE CEREBRO-SPINAL FLUID IN CEREBRO-SPINAL FEVER

GENERAL OBSERVATIONS.—**Pressure.**—The cerebro-spinal fluid is normally present in the subarachnoid space at a certain pressure. It is true that to some extent this pressure may be affected by changes in the blood pressure, etc., but it is by no means dependent upon such factors ; it may and often does vary quite independently. The true cerebro-spinal pressure is the result of the secretory activity of the choroid epithelial cells. Dixon and Halliburton have shown that certain substances promote the flow of cerebro-spinal fluid and bring about an increase of pressure, independently of those substances which affect it secondarily by altering the blood pressure. Such substances are : volatile anaesthetics, extract of choroid gland, excess of carbon dioxide in the blood, etc.

The normal pressure of the cerebro-spinal fluid appears to vary

within wide limits.   According to Peyton Rous, it varied from 70 to
300 mm. of water, while Krönig found it between 120 and 180 mm.
In general, the variations are between 60 and 150 mm. of water;
in the sitting position it may be higher.

For practical purposes the cerebro-spinal fluid in a normal
individual usually flows through a lumbar puncture needle at the
rate of about one drop in 2-3 seconds.

FIG. 33.—Quincke's Spinal
Manometer.

a, vertical limb, 14 cms. in length;
b, horizontal limb; *c*, rubber
tubing (No. 5 size), 40-50 cms.
long, connecting the manometer
tube and *d*; *d*, the connection
which fits into the lumbar
puncture needle.

For method of use see pp. 234-235.

The pressure can be artificially
increased by flexion of the spine,
coughing, crying or compressing the
abdomen ; it also tends to vary
with the respiratory rhythm.

*The Registration of the Cerebro-
spinal Fluid Pressure.*—A number of
instruments have been devised for this
purpose, the simplest of which is that
originally used by Quincke.   This
apparatus is shown in Fig. 33.   The
manometer consists of glass of a calibre
dependent upon that of the lumbar
puncture needle and connected with
the latter by means of a rubber tube.
The height to which the cerebro-spinal
fluid rises in the manometer tube can
be determined with a steel tape
measure.   Sladen and Crohn, however,
introduced a graduated glass tube
giving the readings in mm. water
pressure.   As the inertia of the mano-
meter tube is considerable whichever
variety be used, time must be allowed
to make sure that the fluid reaches
the correct height.   Harvey Cushing, in his experiments on
intracranial pressure, used a mercury manometer, but, as Sophian
points out, the difficulty of sterilising mercury instruments after use
is an objection to their employment in meningitis.

Method of registering the Pressure.—On withdrawing the stylet
from the spinal needle the connection (*d*, Fig. 33) of the manometer
tube is at once inserted into the opening of the needle.   The hori-
zontal limb of the manometer tube is held an inch or two below the
level of the needle until the cerebro-spinal fluid is seen in the mano-

meter tube. The instrument is then raised until the lower arm is on a level with the needle and the height of the column of fluid measured. If the tube is not graduated, this is done by means of a steel tape, zero being made to coincide with the point of the puncture.

A rough estimate of the pressure can be made by noting the rate at which the cerebro-spinal fluid flows through an ordinary lumbar puncture needle into the tube held to receive it.

An increase in the pressure of the cerebro-spinal fluid is usually observed throughout the disease, but more particularly during the earlier part of the course. A marked increase is frequently seen at the first lumbar puncture, that is, when the meninges have actually become infected. Sladen, in observations on the cerebro-spinal-fluid pressure in 75 lumbar punctures in meningitis, found that the average pressure was 327 mm., the highest being 650 mm. The lowest pressure obtained at a first withdrawal was 160 mm., and the average 350 mm. In 15 cases, in which daily observations were made of the intrathecal pressure by Fairley and Stewart, the average was found to be 295 mm. water pressure. Sophian in one case observed a pressure of 830 mm. In one of our cases the pressure was 900 mm. at the first puncture on the third day of illness, while Fairley and Stewart mention one at 1000 mm.

The total amount of cerebro-spinal fluid evacuated bears no constant relation to the intrathecal pressure.

The chief factor in the production of this increased pressure is probably the hyperaemia of the choroid plexuses brought about by inflammatory changes, leading to the increased secretion of cerebro-spinal fluid and a consequent rise in the pressure throughout the subarachnoid space.

The pressure appears only to increase as the meninges become invaded by the organisms. Thus in two cases received early on the first day of illness during the pre-meningeal stage of the disease no definite increase in pressure was observed; the fluids were clear and showed neither an increase in the cellular constituents nor diplococci. In two other cases admitted at a somewhat later stage the cerebro-spinal fluid was also clear to the naked eye but contained numerous diplococci; in both patients the pressure and the quantity of fluid were distinctly increased.

A considerable increase in pressure is usually found in cases punctured for the first time on the second day of disease. Of 21 cases admitted to hospital on the second day of illness, all showed

very marked increase in pressure. The two cases received within the first 6-18 hours, in whom on admission the cerebro-spinal fluid was clear and under no tension, showed within 12 hours a pronounced increase in pressure together with a turbid fluid. The pressure generally appeared rather less in cases punctured for the first time on the third day of illness than in those punctured on the second. Of five cases from whom the cerebro-spinal fluid was obtained for the first time on the fourth day of illness, one only showed a decidedly increased pressure.

Towards the end of the course the pressure shows a distinct tendency to fall, irrespective of whether the case terminates in recovery or death.

Extremely high pressure (600 mm. and over) is seen, as a rule, only in acute cases, and is often accompanied by stupor or active delirium ; it is of no prognostic importance. In the majority of cases there is no direct relationship between the purulency of the fluid evacuated at the first lumbar puncture and its pressure, although occasionally the more purulent fluids are under greater pressure.

Quantity.—The normal amount of cerebro-spinal fluid present in the subarachnoid space is said to vary between 60 and 80 c.c. For practical purposes lumbar puncture in normal individuals seldom yields more than 20 c.c., the average being about 10 c.c.

In cerebro-spinal fever the amount of cerebro-spinal fluid obtained at each lumbar puncture differs widely in different patients. In all our cases the quantity withdrawn was practically the maximum that could be obtained, that is, the fluid was allowed to escape until it ceased to flow through the needle ; this proceeding is perfectly safe. During the pre-meningitic stage of the disease the quantity of cerebro-spinal fluid obtainable is usually comparatively small, but it increases as infection of the meninges proceeds. Thus, in the two cases with clear fluids and no diplococci, mentioned in the preceding paragraph, each yielded only 25 and 30 c.c. respectively. Other patients punctured within 24 to 48 hours of the onset would often give 80-100 c.c. of turbid or purulent fluid. The amount of cerebro-spinal fluid obtained at the first puncture is on an average distinctly greater in cases received on the second day of illness than in those admitted later. The average for 22 second-day cases was 60 c.c. per patient, the maximum obtained being 120 c.c. and the minimum 30 c.c. Twenty cases punctured for the first time on the third day yielded an average of 50 c.c. each, the maximum

being 100 c.c. and the minimum 15 c.c.   In one acute case, however, not admitted until the fourth day, when quite comatose, 110 c.c. of purulent fluid were obtained ; death occurred two days later.

During the course of the disease the quantity of cerebro-spinal fluid obtainable each day often shows a more or less uniform level ; in those cases recovering it is usually smaller in amount during the last few days of the course.   The most we ever obtained at one withdrawal subsequent to the first puncture was 110 c.c. ; this quantity was withdrawn on one or two occasions in four different patients, all acute cases, although not necessarily fatal.

In cases of the progressively purulent type as the cerebro-spinal fluid becomes thicker and more purulent, increasingly smaller quantities of fluid are obtained, until only a few drops can be withdrawn even on aspiration with a syringe.

When internal hydrocephalus appears as a complication, the fluid obtainable by lumbar puncture also diminishes until " dry taps " result.

An increase both in quantity and pressure of the cerebro-spinal fluid is also seen in most other pathological conditions of the central nervous system as well as in acute infections.   Most of the pyrexial patients received as suspected cases of cerebro-spinal fever and in whom lumbar puncture was performed, showed some increase in cerebro-spinal fluid pressure.

Appearance.—The naked-eye appearance of the cerebro-spinal fluid on withdrawal from the subarachnoid space may vary from transparency to almost complete opacity.

In the following description the distinction has been drawn between fluids perfectly colourless and transparent excepting possibly for a few flocculi—called clear ; fluids opalescent, whitish rather than yellow and yielding on standing a small deposit of pus— called turbid ; and finally more opaque fluids, yellowish in appearance and giving a well-marked deposit of pus—purulent.

The solid constituents of pathological cerebro-spinal fluids, such as the turbid and purulent, sink to the bottom of the tube when the latter is allowed to stand, and usually leave a clear supernatant fluid, although often with a distinct yellowish colour, which is especially marked in " purulent " fluids.

Clear fluid is obtained during the pre-meningitic stage of the disease, that is, from within 12 to 48 hours of the onset ; increase in the number of cells is small or absent and diplococci may or may not

be found. In the abortive type of the disease the cerebro-spinal fluid may remain clear throughout, although a few meningococci are sometimes observed.

Turbid fluids are more frequently seen than purulent at the first lumbar puncture. In fulminating cases the fluid is frequently turbid or slightly so, death no doubt occurring before a more abundant reaction has time to develop. Turbid fluids are also the general rule in subacute cases. Of a series of 71 consecutive cases, turbid fluids were obtained at the first withdrawal in 45; of these, 32 recovered and 13 died.

Purulent fluids are sometimes withdrawn in acute cases, either proving fatal or recovering, progressively purulent types and more rarely in subacute cases. Twenty-four of 71 consecutive cases yielded purulent fluids at the first lumbar puncture, 11 recovering and 13 proving fatal.

The Appearance of the Cerebro-spinal Fluid in relation to the Type of the Disease.—*Fulminating Type.*—In accordance with the particular variety of fulminating case (*vide* Chapter VII.) the cerebro-spinal fluid obtained may be only slightly turbid in the one or more purulent in the other. Those cases who appear to succumb from the overwhelming intensity of the blood infection often yield on lumbar puncture a fluid which may be clear or only slightly opalescent; the pressure, however, is usually increased and diplococci are present in variable numbers. These findings correspond with the post-mortem appearances, as in many cases the meningitis is comparatively slight (*vide* Chapter VII. p. 137) and may even amount only to engorgement of the cortical vessels and a dull lustreless pia-arachnoid with relatively few areas of exudate. In the second variety the cerebro-spinal fluid is turbid or purulent, polymorph. cells and meningococci being abundant.

Acute Fatal Type.—The first fluid may be either turbid or purulent. In general, it tends to become more purulent as the disease progresses, and in cases first punctured later than the second day it is almost invariably purulent. It was only on the second day of illness that turbid fluids were obtained in this type of case. As the course continues a fluid at first turbid may become purulent, and afterwards, in contrast to that seen in the progressively purulent type, show little or no tendency to increase in density.

As a rule, the fluid is easily withdrawn throughout the course, 30-60 c.c. flowing readily, until death occurs on the 4th-7th day.

Acute Cases recovering after a Short Course.—Similarly in

these cases the first fluid withdrawn may be either turbid or purulent, unless the patient is seen during the pre-meningitic stage. In all cases the purulency or turbidity decreases from the 3rd to 6th day, becoming less and less turbid until finally it is clear. A yellowish coloration may sometimes persist even when the stage of clarity is reached.

Acute Cases running a Long and Severe Course.—In one case (Case VI. p. 84), which continued acutely ill for 31 days, finally terminating fatally, the cerebro-spinal fluid remained purulent for the first four days; on the fifth it was still yellowish in colour and coagulated almost immediately on standing, forming a large gelatinous clot with very little extraneous fluid. This condition of the cerebro-spinal fluid persisted until the 12th day, after which it ceased to coagulate on standing, but remained very turbid and yellowish in colour until death.

Abortive Type.—Lumbar puncture reveals a cerebro-spinal fluid which is either clear or only slightly turbid; if the latter, it becomes clear within three or four days.

Acute Cases which become Subacute.—The cerebro-spinal fluid, at first either purulent or turbid, subsequently becomes less turbid and then continues to present the same appearance for some time. Not infrequently it becomes bright yellow in colour, and continues to show this change even after it is apparently clear. For instance, in one case recovering after a course of 30 days the cerebro-spinal fluid remained turbid and more or less " whitish " in colour until the 18th day, when it became bright yellow. The yellow colour persisted with varying degrees of turbidity until the 28th day; after this date it rapidly became clear, a yellow tinge, however, still remaining until the 30th day. The fluid was spontaneously coagulable on the 23rd and 24th days, giving a similar appearance to that noted in the acute case previously mentioned.

Progressively Purulent Type.—The cases we have termed " progressively purulent," in preference to the name " suppurative " applied by some authors, show a fluid which may at first be turbid or purulent, but which on subsequent puncturing shows a progressive increase in consistency and amount of solid deposit; the quantity of fluid obtainable also becomes progressively less towards the end, often being too thick to flow through the needle. Of six cases terminating fatally after 9 to 13 days of illness, two cases first punctured on the 2nd and 3rd day respectively yielded a turbid fluid; in the other four, punctured on either the 3rd or 4th days, the fluid

was purulent from the outset. All showed this progressive increase in consistency; in two cases often no fluid was obtainable, and in all during the last three or four days it only amounted to 5-10 c.c. of thick purulent fluid, a few drops only being withdrawn on the last day or two.

Recrudescent Type.—In recrudescent cases the first cerebro-spinal fluid is turbid or purulent according to the severity of the initial stages. With the decline in temperature and the diminution in severity of the symptoms the fluid becomes less turbid and may even become almost clear. We have never, however, observed a recrudescence occur when the cerebro-spinal fluid has once become quite clear to the naked eye with a normal cell content and sterile on culture. During the apyrexial intervals it will be found to show at least a trace of opalescence. With the recrudescence of pyrexia and symptoms the cerebro-spinal fluid increases in turbidity.

Subacute Cases of Moderate Severity.—As a general rule the first fluid obtained is turbid only, although more rarely it may be definitely purulent. Of 13 such subacute cases, the fluid withdrawn at the first lumbar puncture was turbid in 10 and purulent in three. All the cases recovered, the turbidity of the fluid gradually becoming less and less until it disappeared.

Subacute Cases—Mild.—The cerebro-spinal fluid exhibits a slight or moderate degree of turbidity; in some it may merely amount to a trace of opalescence.

Cases which become Chronic.—As a case passes into a chronic stage the fluid becomes less turbid in appearance, and during the subsequent course may often appear almost clear. Should hydrocephalus develop, especially in the posterior basic type of infants, lumbar puncture may yield a fluid clear to the naked eye. The possibility of cases of cerebro-spinal fever coming under observation for the first time at this stage being mistaken for cases of tuberculous meningitis is alluded to elsewhere (*vide* Chapter XII. p. 330). Not only may the fluid appear clear, but on microscopical examination the lymphocyte will be found to be the predominant cell. Frequently the fluid is yellowish in appearance, the colour varying from pale straw to bright yellow.

TABLE V

SHOWING THE APPEARANCE OF CEREBRO-SPINAL FLUID OBTAINED AT THE FIRST WITHDRAWAL IN RELATION TO THE TYPE OF CASE (75 CASES)

	Number of Cases.	Clear.	Turbid.	Purulent.
Fulminating cases (fatal) . .	5	–	4	1
Acute fatal cases . . .	11	–	4	7
Acute cases recovering after a short course	13	1	8	4
Acute cases becoming subacute or running a long and severe course :				
(a) Non-fatal . . .	5	2	1	2
(b) Fatal	1	–	–	1
Progressively purulent cases (fatal)	6	–	2	4
Recrudescent cases :				
(a) Non-fatal . . .	7	–	6	1
(b) Fatal	2	–	2	–
Subacute cases with a long course or becoming chronic :				
(a) Non-fatal . . .	4	1	3	–
(b) Fatal	1	–	1	–
Subacute cases of a moderate severity (non-fatal) . .	13	–	10	3
Subacute cases with a mild course (non-fatal) . . .	5	–	5	–
Abortive cases (non-fatal) .	2	1	1	–
Total	75	5	47	23
Recovered	50	5	34	11
Died	25	0	13	12

Supernatant Part of Fluid on Standing.—As a rule in a purulent fluid on standing the supernatant portion is yellow rather than colourless, and, as we have observed, this colour is frequently noted throughout the course of acute cases. In experiments, we have succeeded in abstracting it only partly with chloroform, from which, however, it fades very quickly ; the coloration usually accompanies a large amount of protein and a well-marked Noguchi globulin reaction.

Blood-stained Fluids.—Blood may often be found present in the cerebro-spinal fluid withdrawn by lumbar puncture. Its presence may be due to any of the following causes :

(a) A vessel in the subcutaneous tissue may be pricked during the passage of the needle from the surface of the skin to the sub-

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arachnoid space. When this occurs a few drops of blood will escape first through the needle and usually be followed by cerebro-spinal fluid free from blood.

(b) If the needle is pushed in too far it may puncture the venous plexus lying on the ventral aspect of the spinal cavity. This accident is usually followed by a copious flow of blood, and the cerebro-spinal fluid withdrawn may remain deeply blood-stained throughout its flow, resembling almost pure blood; such a fluid rapidly clots on standing. Occasionally it may become clearer towards the end of the flow. For the few days following this accident the cerebro-spinal fluid may continue to appear blood-stained, gradually fading sometimes to an orange colour, sometimes to yellow.

(c) Blood may appear at the end of the flow with the last few c.cms. of fluid. In this case, especially if the pressure of the cerebro-spinal fluid has been somewhat high, it is probably due to the rupture of congested venules or capillaries in the subarachnoid space, owing to the sudden relief of the pressure of the fluid from their exterior.

(d) The fluid may be uniformly haemorrhagic owing to the extreme intensity of the inflammation; this is seen only in acute fatal types and occasionally in fulminating cases. The fluid, on standing, may not clot.

In the first three of the above instances the presence of blood is of no significance, but in the latter the prognosis is most unfavourable.

CHEMICAL CHARACTERS

REACTION.—The normal alkalinity of the cerebro-spinal fluid during meningitis tends markedly to diminish. According to Kopetzky, this decrease in the alkaline reaction is due to the presence of a combined acid; the presence of lactic acid has also been demonstrated. There is some diversity of opinion, however, as to whether the cerebro-spinal fluid during the acute stages gives a faintly alkaline reaction or becomes slightly acid. Results may vary with the indicators used. In our investigations the three following indicators have been employed: (a) Litmus (paper and solution), (b) Phenolphthalein (0·5 per cent in 50 per cent alcohol), (c) Methyl orange.

Clear fluids withdrawn during the pre-meningitic stage are invariably alkaline.

(a) *Litmus*.—Tested with litmus the cerebro-spinal fluid gave

an alkaline reaction of varying degree in nearly all cases, no matter at what stage of the disease ; it was very faint in the early part of the illness and also in acute fatal cases, especially when pus was present in quantity.   In cases progressing favourably, the alkalinity of the fluid gradually increases with its progress towards normal appearance and constitution.   In only a few instances did the fluid appear neutral to litmus, and in two a faintly acid reaction was obtained ; the latter as seen during the first few days in an acute fatal case dying within seven days, and on the sixth and seventh day in an acute case recovering after a 14 days' course.   In these instances no alkaline reaction was obtained with phenolphthalein. The alkalinity of the fluid according to litmus tends to increase on standing ; one purulent fluid, very faintly alkaline on withdrawal, was very markedly alkaline a month later.   The apparently neutral fluids mentioned above were also definitely alkaline to all reagents two months later.   Litmus, however, appears too rough an indicator for such fine shades of testing.

(b) *Phenolphthalein* (0·5 *per cent in* 50 *per cent Alcohol*).—This is a considerably more delicate indicator.   With its use no alkaline reaction was observed in 28 fluids out of about 400 so tested ; the remainder gave a very faintly pinkish coloration.   This apparent absence of alkalinity was usually associated with a more or less purulent fluid.   It was found in some acute fatal cases at the beginning or the end of the course, occasionally during the first few days in acute cases recovering, and also in a few subacute cases of moderate severity.   In all cases recovering, the fluid regained its alkalinity in from one to four days.   Table VI. on the following page illustrates the cases.

In none of the fluids failing to show an alkaline reaction with phenolphthalein was an acid reaction obtained with litmus or methyl orange ; with litmus, each, with the exception of four giving a neutral reaction, appeared very faintly alkaline.

In order to determine the possible presence of slight acidity in those cerebro-spinal fluids failing to give an alkaline reaction with phenolphthalein, we conducted tests which are illustrated by the following examples :

(1) The cerebro-spinal fluid to be tested was placed in a small porcelain dish and a few drops of the phenolphthalein (0·5 per cent in 50 per cent alcohol) added.   From a small burette a decinormal solution of sodium hydrate was allowed to drop into the mixture, each drop being 1/18 c.cm.   As soon as the first drop reached the cerebro-spinal

fluid and phenolphthalein in the dish a pink colour was seen, which disappeared, however, on stirring with a glass rod. It was found that 3/18 c.cm. of N/10 sodium hydrate were necessary for the fluid to reach slight alkalinity, as indicated by the appearance of a very faint pinkish tinge.

(2) To 10 c.cm. of the cerebro-spinal fluid (the purulent fluid from an acute case) two or three drops of phenolphthalein (0·5 per cent in 50 per cent alcohol) were added; no pink tinge resulted; 4/18 c.cm. of a decinormal solution of sodium hydrate, however, added to this mixture

TABLE VI

THE CEREBRO-SPINAL FLUID : REACTION WITH PHENOLPHTHALEIN

(Alkalinity = +. No Alkalinity = −).

	Day of first Puncture.	Result, etc.	Days of Puncture.						
			2nd.	3rd.	4th.	5th.	6th.	7th.	8th.
Acute fatal cases	4th day	Died 6th day	.	.	−	+	−	.	.
	2nd ,,	,, 5th ,,	−	−	+	−	.	.	.
	2nd ,,	,, 4th ,,	−	+	−	.	.	.	.
	3rd ,,	,, 4th ,,	+	−	.	.	.	.	.
Acute cases re-	3rd ,,	Recovered 8th day	+	−	+	+	+	+	+
covering	2nd ,,	,, 14th ,,	−	−	+	+	+	+	+
	2nd ,,	,, 14th ,,	−	−	−	−	+	+	+
	2nd ,,	,, 10th ,,	−	−	+	+	+	+	+
	4th ,,	,, 14th ,,	.	.	+	+	−	−	+
	3rd ,,	,, 10th ,,	−	−	−	+	+	+	+
	2nd ,,	,, 40th ,,	−	+	−	+	+	+	+
		(became subacute)							
Subacute cases	4th ,,	Recovered 10th day	−	+	+	+	+	+	+
(moderately	3rd ,,	,, 14th ,,	+	−	−	+	+	+	+
severe)	9th ,,	,, 18th ,,	−	+	+	+	+	+	+

at once produced a deep pink coloration. A slightly smaller quantity (2/18 c.cm.) of decinormal sulphuric acid was necessary to neutralise this and destroy the pink coloration. According to this test, therefore, the cerebro-spinal fluid was slightly acid to the extent of 2/18 c.c. N/10 acid per 10 c.c. of fluid.

By these methods slight acidity was detected in 18 of the 28 fluids failing to give an alkaline reaction with phenolphthalein; in all instances the cases were acute.

In such an indirect method everything depends, of course, upon the assured accuracy of the decinormal solutions used.

Fairley and Stewart, in testing a large series of cerebro-spinal fluids by means of litmus and Henderson's reagent (used to detect slight grades of acidity), failed to detect at any time a slight acid

reaction. Neutrality was occasionally met with. It has been pointed out, however, that litmus is not a sufficiently delicate indicator for use with cerebro-spinal fluids. Henderson's reagent (Dinitrohydroquinone) is of a bright orange colour in distilled water, and changes on the addition of moderately strong alkali to deep purple ; in the presence of an acid of similar strength the orange colour changes to pale greenish-yellow. In the presence of slight acidity, however, it is said to become orange-yellow before the green-yellow stage is reached. In comparison with such colorimetric methods, however, we consider that the above volumetric determination with phenolphthalein as an indicator gives more accurate results.

(c) *Methyl Orange*, used in a few instances, was found not sufficiently delicate for such work.

In all cases which recover the fluid becomes increasingly alkaline until the normal level is reached.

Conclusions.—(1) In the vast majority of cases, the normal alkaline reaction of the cerebro-spinal fluid is diminished but not abolished during the earlier stages of meningitis. As the case recovers or becomes subacute the alkalinity increases towards normal ; in acute fatal cases it remains diminished or may be absent.

(2) Occasionally the alkalinity of the cerebro-spinal fluid is diminished to such an extent that the fluid gives a neutral reaction.

(3) In a few acute cases the fluid may be very slightly acid.

PROTEINS.—From the commencement of meningitis there is an increase in the protein content of the cerebro-spinal fluid throughout the disease. With a turbid or purulent fluid this, of course, is to be expected, but if the supernatant fluid, after centrifugalisation, alone be tested, it will be found rich in protein. The increase in protein content can be demonstrated by the following tests :

(1) *Acetic Acid Test* (*Moritz*).—This test consists in the appearance of white cloud or precipitate when a few drops of 5 per cent acetic acid are added to 2 c.c. of cerebro-spinal fluid.

(2) *Nitric Acid Test* (*Runeberg*).—A few drops of chemically pure nitric acid are added to a small quantity of cerebro-spinal fluid ; inflammatory fluids give a heavy white cloud. The ring test consists in layering the cerebro-spinal fluid over the nitric acid, when a similar white cloud appears at the junction of the two fluids.

(3) *Nonne's Test*.—Cerebro-spinal fluid and a heat-saturated solution of ammonium sulphate are added together in equal parts, leading to precipitation of the globulins. This phase occurs in every cerebro-spinal fluid including the normal. The mixture, after allowing to stand

for three minutes, is then filtered ; to the filtrate is added one drop of dilute acetic acid and the mixture boiled. If a cloud appears, due to serum albumin, the test is considered positive.

(4) *Braun and Husler's Test for Serum Globulin.*—To 1 c.c. of cerebro-spinal fluid N/300 hydrochloric acid (one part of normal HCl to 299 parts of distilled water) is added slowly, shaking constantly. If clouding does not occur after 5 c.c. have been added, the reaction is negative. When positive, the reaction usually takes place within a few minutes, although in some instances the tube must be allowed to stand for half an hour.

(5) *Noguchi's Globulin Test.*—This is the most important of the gross chemical tests, and a positive result indicates a pathological increase in the protein content of the cerebro-spinal fluid.

To one part of cerebro-spinal fluid is added 5 parts of a 10 per cent solution of butyric acid in physiological salt solution and the resulting mixture boiled. One part of a 4 per cent solution of sodium hydrate is then quickly added and the mixture again boiled. With normal cerebro-spinal fluid a slight, whitish, and diffuse cloud is produced which does not precipitate. In the presence of an increased protein content a heavy white cloud is produced, which on standing precipitates in the form of large flocculi. The mixture, after the final boiling, should be allowed to stand for an hour before noting the result.

In carrying out the following series of observations the Noguchi test has chiefly been employed.

In clear fluids obtained during the pre-meningitic stage of the disease, the results of testing for an increase in protein content are somewhat variable. If diplococci are present, however, Noguchi's test usually gives a slight positive reaction, although no definite increase in the cell content may be apparent. In fluids free from organisms the test is often negative ; in one case, however, admitted from within 5 to 6 hours of the onset and yielding on lumbar puncture a clear fluid showing neither organisms nor increase in cells, the Noguchi test was weakly positive after allowing the tube to stand for an hour.

In the clear supernatant portion of a cerebro-spinal fluid containing deposit the protein content is greatly augmented. This increase is chiefly in globulin but the albumin is also affected. In purulent fluid a large coagulum can often be obtained on boiling alone.

At the end of the course in a favourable case, when the fluid is quite clear to the naked eye and a few mononuclear cells only are visible on microscopical examination of the centrifugalised deposit, we find that a relative increase in the protein content of the fluid

may still persist ; this, however, gradually diminishes during the ensuing 5 or 6 days, until, according to Noguchi's test, the protein content again reaches the normal. Before testing it is necessary to exclude the presence of blood by a search for possible red blood corpuscles in the deposit. The following table shows the results in some of the fluids tested, and illustrates the general principles :

TABLE VII

SHOWING THE PROTEIN TESTS IN CLEAR CEREBRO-SPINAL FLUID
ON AND AFTER RECOVERY

The day of recovery from actual meningitis in this instance is taken as the first day on which a perfectly clear cerebro-spinal fluid was obtained.

Type of Case.	Day of Recovery.	Number of Days after Recovery that C.-s. Fluid was obtained and tested.	Appearance of the C.-s. Fluid.	Centrifugalised Deposit.	Noguchi Test.
Acute case recovering after short course	10th	Tested on day of recovery	Clear	One or two small lymphocytes	Strongly +
Subacute case (moderate)	15th	,,	,,	Ditto	Weak +
Subacute case (severe)	18th	,,	,,	A few lymphocytes and an occasional polymorph	Strongly +
Acute case recovering after a long course	10th	1	,,	One or two lymphocytes	Weak +
A second acute case recovering after a short course	10th	1	,,	Ditto	Strongly +
An acute case with recrudescence recovering on 24th day	24th	1	,,	A few lymphocytes	Weak +
Subacute case (moderate)	14th	2	,,	One or two small lymphocytes	Very weak +
Acute case recovering	10th	4	,,	Ditto	Very weak +
Subacute case (moderate)	14th	4	,,	Ditto	Very weak +
Subacute case (severe)	18th	10	,,	Ditto	Nil

Quantitative Estimation of Albumin Content.—Bybee and Lorenz adopted Brandenburg's method of estimating albumin in urine for

use in relation to the cerebro-spinal fluid. A two-armed tube is taken and nitric acid placed in one side, and cerebro-spinal fluid on the acid in the other arm. The normal amount of albumin averages 0·01 per cent to 0·06 per cent ; by the above method it was found in meningitis to be increased to 0·2–0·3 per cent and occasionally more.

FIBRIN CONTENT.—A rough estimation of the fibrin content of the fluid in meningitis can be made by allowing the cerebro-spinal fluid to stand unshaken in a test-tube for several hours after withdrawal, preferably at room temperature.

Normal cerebro-spinal fluid and transudates do not show any appreciable formation of fibrin ; the fluid in purulent meningitis, however, exhibits a varying quantity of fibrin network after standing. In fluids only slightly turbid, after one or two hours, a thin delicate coagulum will frequently be observed extending up the centre of the fluid.

Spontaneously Coagulable Fluids.—Occasionally a fluid almost immediately after withdrawal or on standing for a short time will form a large opalescent coagulum, a very small quantity only of extraneous fluid remaining. This latter is extremely rich in both albumin and globulin but the bulk appears to be fibrin. Otherwise the fluid shows only a few cells, polymorphonuclear or mononuclear, and meningococci may or may not be present.

A fluid spontaneously coagulable was withdrawn in four of our cases, usually late in the disease ; three of the cases recovered and one died. The day of appearance of this condition in each case was as follows :

Acute case terminating fatally after
   a long course (31 days) .   .   5th-12th days of disease inclusive.
Acute case recovering after a long
   course (40 days)   .   .   .   27th day.
Two subacute cases recovering—
   (1) After 18 days .   .   .   16th and 17th days.
   (2) After 28 days .   .   .   23rd and 24th days.

In the cerebro-spinal fluids of the above cases, on the days mentioned meningococci were present only in one case, that proving fatal ; also one only showed the presence of a few red blood corpuscles.

The causes leading to the production of such a fluid are obscure. Each case had previously received several doses of anti-meningococcal serum.

GLUCOSE.—Normal cerebro-spinal fluid contains a reducing substance, now definitely known to be glucose, which can readily be detected by means of Fehling's solution. In the acute stages of cerebro-spinal fever this reducing substance is absent or in quantities so minute as to show on boiling with Fehling's solution no reduction. Authors have differed in their views as to the value to be attached to this test ; in our own experience of cerebro-spinal fever it has undoubtedly been of value as an indication of the patient's progress.

Method of Testing.—The reaction is best seen when about 2 c.cm. of the cerebro-spinal fluid to be examined is heated to boiling point with 6-8 drops of freshly prepared Fehling's solution—that is the No. 1 and No. 2 fluids mixed and boiled before using. In positive cases a reddish or yellowish-brown precipitate appears usually at once ; in other cerebro-spinal fluids, if the reaction is very faint, it is seen only as a small deposit after allowing the tube to stand. If too much Fehling's solution be used the reaction may not appear. Fluids giving a negative result usually become a deep purple colour.

As the method of treatment in the greater number of our cases consisted in daily lumbar puncture following a certain period of intrathecal serum administration, until a normal cerebro-spinal fluid was obtained, we were enabled to examine the fluid withdrawn from day to day until the termination of meningitis. The cerebro-spinal fluid was tested for the presence of glucose throughout the course in 50 consecutive cases.

Clear fluids obtained during the pre-meningitic stage, that is before the appearance of definite meningitis, invariably show the presence of glucose. In three such cases (one of which is not included in the following analysis of fluids) admitted within 6-18 hours of the onset of illness, each yielded a clear fluid showing no increase in the cell content ; one contained a fair number of Gram-negative diplococci. All three, however, gave a well-marked glucose reaction. Within 12 hours, in each case, the cerebro-spinal fluid was turbid and glucose could not be detected.

The glucose reaction in relation to the type of case is shown as follows :

(1) *Fulminating Types.* (2 cases—each died within 36 hours of the onset.)—No glucose was present in the cerebro-spinal fluid of either case.

(2) *Acute Fatal Type.* (8 cases—death in 4-7 days.)—In all, the glucose reaction was absent throughout the course.

(3) *Acute Cases recovering after a Short Course.* (13 cases—8-14 days.)

The presence or otherwise of glucose is shown in the following table :

TABLE VIII

ACUTE CASES RECOVERING AFTER A SHORT COURSE—GLUCOSE REACTION

(+ = glucose present—slight reaction ; + + = glucose present—well-marked reaction ; − = glucose absent.)

Case.	Duration of Course. Days.	Day of Disease on which first Lumbar Puncture was performed.	Results of Glucose Test. Days of Disease.												
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	6	1st (early) clear fluid	+	−	−	+	+	+	.	.	.	.	.	.	.	.
2	7	1st (late)	−	−	+	+ +	+ +	+ +	+ +	.	.	.	.	.	.	.
3	8	2nd	.	−	+	+ +	+ +	+ +	+ +	+ +	+ +	.	.	.	.	.
4	9	2nd	.	−	+	+ +	+ +	+ +	+ +	+ +	+ +	+ +	.	.	.	.
5	9	2nd	.	−	−	−	+	+ +	+ +	+ +	+ +	+ +	.	.	.	.
6	10	2nd	.	−	+	+	+ +	+ +	+ +	+ +	+ +	+ +	+ +	.	.	.
7	10	3rd	.	.	−	−	+ +	+ +	+ +	+ +	+ +	+ +	+ +	.	.	.
8	10	3rd	.	.	−	−	−	−	+	+ +	+ +	+ +	.	.	.	.
9	12	1st (late)	−	−	+	+	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	.	.
10	13	2nd	.	−	−	−	−	−	−	+	+ +	+ +	+ +	+ +	+ +	.
11	14	1st (late)	−	−	−	+	+	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
12	14	2nd	.	−	+	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
13	14	4th	.	.	.	−	−	−	−	−	−	+	+ +	+ +	+ +	+ +

In those cases (Nos. 1, 2, 9, and 11) mentioned as being first punctured on the 1st day of illness, Cases 2, 9, and 11 were received into hospital within about 18-24 hours of the onset ; in each case a turbid or purulent fluid was obtained on lumbar puncture. In Case 1, however, the puncture was performed during the pre-meningitic stage, the patient coming under observation within a few hours of the onset ; 10-12 hours later, the cerebro-spinal fluid was turbid and no glucose could be detected.

In all cases the reappearance of glucose in the cerebro-spinal fluid was associated with clinical improvement, and in no case did it again disappear. No definite indication of the absence or presence of glucose can be drawn from the appearance of a deposit of pus in the fluid, although in markedly purulent fluids, such as those seen in the acute fatal and progressively purulent types, it is invariably absent.

The actual presence of meningococci, which ferment glucose, bears no definite relation to the absence of this substance from the cerebro-spinal fluid. Of the above cases meningococci were seen on direct examination in the presence of a positive glucose reaction on the following days :

> In Case 3 on the 3rd day (glucose present).
> In Case 4 on the 3rd, 4th, and 5th days (glucose present).
> In Case 12 on the 3rd and 4th days (glucose present).

The number of organisms, however, showed a considerable decrease in fluids giving a positive reaction, and failed to grow on culture. In one mild sub-acute case, however, admitted on the 5th day of illness, the first puncture fluid gave a positive glucose reaction, and in addition yielded a fair growth of meningococci.

(4) *Acute Cases running a Long and Severe Course or becoming Subacute.*   (4 cases : 24-40 days.)

CASE 1 (24 days).	Originally acute, became subacute —recovered.	No glucose was detected until the 8th day of illness when a faint positive reaction was obtained. It was well marked on the 9th day and did not again disappear. Meningococci were found present in the fluid, however, until the 17th day.
CASE 2 (23 days).	Originally acute, became subacute —recovered.	The glucose reaction was absent until the 9th day ; it was present on the 10th, but again disappeared on the 11th coincidently with the appearance of hydrocephalic symptoms. Glucose returned, however, on the 14th day and persisted.
CASE 3 (40 days).	Originally acute, became subacute —recovered.	No glucose was apparent until the 30th day ; having once returned it did not again disappear. Its return in this instance more or less coincided with the gradual disappearance of hydrocephalic symptoms consequent to increased amounts of cerebro-spinal fluid being obtained on repeated lumbar puncture.
CASE 4 (31 days).	Remained acutely ill throughout course—fatal.	The glucose reaction was absent throughout with the single exception of the 18th day, when it was found to be exceedingly faint. Its presence was unassociated with any apparent change in the clinical condition of the patient.

(5) *Abortive Cases.*—In the cerebro-spinal fluid of an abortive case, obtained early on the 2nd day, the glucose reaction was positive.

(6) *Progressively Purulent Types.* (5 cases : death in 9-14 days.) —In all five the glucose reaction was absent throughout the course.

(7) *Recrudescent Cases.*   (5 cases : 16-80 days.)

CASE 1 (15 days). The cerebro-spinal fluid, first obtained on the 2nd day of illness, showed an absent glucose reaction until the 4th day. From this time onwards it did not again disappear, remaining faintly marked, in spite of a recrudescence lasting from the 9th day until the 13th inclusive. On the 14th day it was well marked.

CASE 2 (16 days). The glucose reaction returned on the 9th day, and was strongly positive on the 10th. This was associated with well-marked clinical improvement and a disappearance of meningococci from the cerebro-spinal fluid. An intercurrent pneumonia, however, commencing on the evening of the 8th day, was followed by a recrudescence of meningitis, and meningococci again appeared in the cerebro-spinal fluid on the 11th day with an absence of glucose ; it remained absent until death.

CASE 3 (17 days). A positive reaction was not found until the 7th day, when it persisted until the 9th, disappearing during a recrudescence from the 10th to the 13th day inclusive, then reappearing.

CASE 4 (24 days). An abortive attack occurred, followed by a recrudescence four days later ; the patient was not under our observation during the abortive attack. The glucose reaction remained absent until the 5th day of the recrudescent attack. It then persisted until the 18th day of total illness, disappearing again during a further recrudescence from the 19th to the 21st day inclusive ; on the 22nd day glucose was again present and did not disappear.

CASE 5 (80 days). No glucose reaction was detected until the 34th day of illness ; it never again disappeared in spite of several recrudescences of 1-4 days' duration.

(8) *Subacute Case* (*Mild and Moderately Severe*). (8 cases : 18 days or less.)—The results in these cases are shown in the following table :

(+ = slight reaction ; + + = well-marked reaction ; − = glucose absent.)

	Day of first Lumbar Puncture.	Day of Disease on which a clear Cerebro-spinal Fluid was first obtained.	Results of Glucose Reactions. Days of Disease.						
			1	2	3	4	5	6	
Case 1	(Mild) 4th	8th	.	.	.	−	+	+ +	In all
,, 2	,, 5th	8th	.	.	.	.	+	+ +	cases
,, 3	,, 3rd	10th	.	.	−	+	+ +	+ +	glucose
,, 4	,, 3rd	12th	.	.	−	−	+ +	+ +	was
,, 5	,, 3rd	12th	.	.	−	−	+ +	+ +	present
,, 6	,, 3rd	14th	.	.	−	−	+ +	+ +	after
,, 7	,, 3rd	15th	.	.	−	−	−	+	the 6th
,, 8	,, 3rd	16th	.	.	−	−	−	+	day.

Again the presence of meningococci bore no relation to the absence of glucose, although the organisms were very few in number when the fluid gave a positive reaction. In Case 2 the first fluid, obtained on the 5th day, in addition to showing a few pairs of meningococci on direct microscopical examination, yielded a fair growth in culture ; glucose was present.

(9) *Subacute Cases running a Long Course.*

CASE 1 (30 days). Admitted and punctured within five hours of the onset ; the first fluid was clear and contained no meningococci, nor did it show an increased number of cells. The glucose reaction was well marked. Next day the cerebro-spinal fluid was turbid, but Fehling's solution still revealed the presence of the reducing sugar. The case recovered after a course of 30 days, the glucose reaction being present throughout.

CASE 2 (18 days). Admitted 9th day ; glucose reaction previously absent returned with clinical improvement on the 14th day.

CASE 3 (46 days). Admitted 13th day ; glucose reaction present throughout although faint from the 13th to the 22nd day.

CASE 4 (28 days). Admitted 14th day ; glucose reaction previously absent returned on the 25th day with the gradual disappearance of symptoms of hydrocephalus.

In pneumococcal, staphylococcal, and streptococcal meningitis, glucose almost invariably disappears from the cerebro-spinal fluid. In tuberculous meningitis, however, it is usually present.

Conclusions.—(1) During the stage of the disease that precedes definite meningitis, the glucose in the cerebro-spinal fluid is unaffected.

(2) Glucose is absent throughout the course in acute fatal types, and usually also in progressively purulent types.   In fulminating cases it is more often absent than present.

(3) If the patient remains acutely ill glucose is persistently absent.

(4) In acute cases recovering after a short course, glucose, absent during the earlier days, reappears as the patient improves.

(5) In mild or subacute cases glucose may be present throughout the course, though more frequently it is absent during the first few days.

(6) The return of glucose to the cerebro-spinal fluid is never accompanied by an increase in the intensity of meningitis.

(7) In cases of a recrudescent type there may be a return of glucose with clinical improvement, and a subsequent disappearance during the recrudescence.

(8) In the presence of a complicating hydrocephalus a positive glucose reaction is of no prognostic value.

(9) The disappearance of glucose from the cerebro-spinal fluid does not appear to depend upon the presence of meningococci.   It may be present when these organisms are both visible on direct examination and obtainable in culture.

Potassium Permanganate Tests.—In 1910 Mayerhofer described a relative quantitative reduction of potassium permanganate when added to cerebro-spinal fluid in an acid solution on boiling. His general conclusions were that in normal fluids the reduction index is low, while in those from patients suffering from meningitis it is high (3-8).

Every cerebro-spinal fluid brings about a gradual reduction in potassium permanganate whether acid be present or not ; and since in pathological fluids reduction takes place more rapidly than in normal fluids, various modifications of the test have been applied. Thus P. Boveri in 1914 claimed to be able to distinguish between normal and pathological fluids by means of the following reactions :

(1) **The Zonal Reaction.**—In a small test-tube 1 c.c. of 0·01 per

cent potassium permanganate solution is added to 1 c.c. of cerebro-spinal fluid in such a way as to form layers, that is, the solution is allowed to trickle down the side of the tube held in a slanting position. On holding the tube upright a more or less bright yellow ring is observed at the junction of the two fluids provided the cerebro-spinal fluid is pathological; if it is normal there is no yellow coloration.

(2) **The Global Reaction.**—When the above reaction is determined the two fluids are shaken together in the tube in order to mix them. In normal cerebro-spinal fluids the pink rosy colour lasts for a considerable time. If the fluid is pathological the colour changes to one of bright yellow in from a few seconds to a few minutes; the reaction is strong when this change occurs within 2 minutes, medium when it occurs in 3 or 4 minutes, and weak when it requires 5 or 6 minutes. When this latter time is exceeded the reaction may be regarded as negative.

The reactions are said not to vary with lymphocytosis and often to be well marked when cells are relatively scanty. The actual cause of the increased rapidity of reduction of permanganate is uncertain; Boveri suggests that since it often co-exists with positive reactions of Nonne and Noguchi, it probably depends upon changes in the cellular activities of albuminous substances, and possibly on the decomposition of endogenous albumin.

One of us (C. W. D.), having tested these reactions on the cerebro-spinal fluid in all varieties of disease of the central nervous system, including dementia paralytica, tabes dorsalis, disseminated sclerosis, poliomyelitis, etc., has found that apart from meningitis both re-actions are unreliable and frequently give negative results when Noguchi's test is positive; consequently we cannot agree with its author that the test is more delicate than those hitherto in use. In meningitis the reaction is invariably positive, and in turbid fluids the global reaction often occupies less than half a minute. When, however, the cerebro-spinal fluid is obviously pathological to the naked eye, the application of the test is scarcely indicated.

We have found Boveri's reaction of some value under the following circumstances:

(1) The zonal reaction in testing the clear fluid obtained on lumbar puncture during the pre-meningitic stage of cerebro-spinal fever.

(2) The global test used purely as a time reaction for ascertaining the progress of the case.

Clear Fluids obtained during the pre-Meningitic Stage.—One

patient punctured within 5-6 hours of the onset yielded a clear fluid free from meningococci and cytological increase. Boveri's reaction gave the following result :

> Zonal = Positive after 2 minutes.
> Global = Still negative after 6 minutes (the pink colour changed to yellow in 15 minutes).

A second clear fluid obtained on the first day from a case of cerebro-spinal fever showed on microscopical examination the presence of a few Gram-negative diplococci but no increase in the cellular constituents.

Boveri's reaction gave the following result :

> Zonal = Positive in a few minutes.
> Global = Still negative in 6 minutes (the pink colour did not change to yellow until 24 minutes had elapsed).

It will thus be seen that the zonal reaction was positive in each case while the global reaction was negative ; in the latter, however, the time occupied in reducing the permanganate solution was considerably less than in the case of normal fluids. W. J. Denehy, also, in testing similar clear fluids, frequently found a positive permanganate reaction in the absence of any other abnormality.

Consequently the zonal reaction may be of some value if early cerebro-spinal fever is suspected, although occasionally the cerebro-spinal fluid obtained from pyrexial patients suffering from diseases other than meningitis may give a slightly positive zonal reaction (*e.g.* pneumonia). Also, the test is valueless in the presence of blood, however minute the quantity. If a fluid be positive, therefore, care should be taken to exclude the presence of blood by a microscopical examination of the centrifugalised deposit.

Clear Fluids obtained at the Termination of Meningitis.—The first clear cerebro-spinal fluid obtained from a recovered case of cerebro-spinal fever can be shown to be somewhat abnormal by the presence of a positive zonal reaction. Frequently the global reaction is also positive within 6 minutes ; when absent, however, there is usually exhibited a considerable decrease in the time occupied, as compared with the normal, in the change of colour. As we have shown in the section dealing with the increase in protein content (p. 246), Noguchi's globulin test as a rule is also positive. Both the latter and the positive permanganate reaction disappear within a few days.

The following table illustrates some of the results we obtained :

TABLE IX

Showing the Permanganate Reactions in Clear Cerebro-spinal Fluids withdrawn on Recovery from Cerebro-spinal Fever

In all cases the fluid was clear and transparent, and microscopical examination of the centrifugalised deposit showed the presence of only a few lymphocytes.

Number of Days after Recovery on which the Clear Fluid was examined.	Type of Case.	Day of Disease on which a Clear Fluid was first obtained (=Recovery).	Boveri's Reaction.	
			Zonal.	Global.
Day of recovery . .	Acute	10th	+ faint	5 minutes
,, ,, . .	,,	14th	+ ,,	3 ,,
,, ,, . .	Subacute	16th	+ ,,	3 ,,
,, ,, . .	Recrudescent	24th	+ ,,	10 ,,
,, ,, . .	Subacute	46th	+ ,,	2½ ,,
Day after recovery	Acute	14th	+ ,,	2½ ,,
,, ,,	Subacute	16th	Negative	4½ ,,
2 days after recovery	,,	14th	+ faint	12 ,,
,, ,,	,,	32nd	Negative	4½ ,,
4 days after recovery	Acute	10th	Negative	10 ,,
6 days after recovery	Subacute	16th	Negative	25 ,,

Purulent and Turbid Fluids. (Fluids pathological to the naked eye.)

The supernatant part of the fluid, once the deposit had settled, was used for the test. In some 500 fluids the result was invariably a positive global reaction. The colour usually changed to yellow in from a few seconds to one minute; in merely turbid fluids it occupied from 1 to 3 minutes, and occasionally 4 minutes, when the fluid was only slightly turbid.

The zonal reaction was frequently inconclusive owing to the yellow colour of the supernatant part of the cerebro-spinal fluid. In some instances, however, the ring appearing at the junction of the two fluids was of even a brighter yellow than that of the cerebro-spinal fluid.

The Global Reaction used purely as a Time Reaction for estimating Progress.—The fact that the pink colour disappears almost immediately or within a few seconds in purulent or very turbid fluids, and occupies a longer period as the fluid becomes clearer, suggested that the test might be of some use as an index of improvement. As a result of experiment we found that as a time index it is only of value in acute and subacute cases running a short course.

In acute fatal cases, and those of a progressively purulent type, the global reaction seldom occupied more than 1-2 minutes in yielding a positive result; the period, however, did not show a steady and definite diminution throughout the course, and consequently

was of no value as an indication that the patient was becoming steadily worse.

Acute and subacute cases running a long course gave variable results, the reaction varying to a certain extent with the appearance and constitution of the cerebro-spinal fluid, and from which no definite conclusions could be drawn.

TABLE X

PERMANGANATE TEST USED AS A TIME REACTION

Acute and Subacute Cases recovering after a Short Course

The global reaction showed a progressive decrease in many cases, the following serving as examples. The supernatant portion of the centrifugalised cerebro-spinal fluid only was used in the test. Six cases in which the cerebro-spinal fluid was tested daily gave the following results—

Acute case.	First clear fluid obtained on 10th day = Progressive increase in time occupied in global reaction from a few seconds on the 3rd day to 5 minutes on the 10th day.
Acute case.	First clear fluid obtained on the 10th day = Progressive increase in time occupied in global reaction from $\frac{1}{2}$ minute on the 2nd day to 5 minutes on the 10th day.
Acute case.	First clear fluid obtained on 14th day = Progressive increase in time occupied by global reaction from $\frac{1}{2}$ minute on 2nd day to 3 minutes on 14th day.
Acute case.	First clear fluid obtained on 14th day = Progressive increase in time occupied by global reaction from a few seconds on 1st day to $2\frac{1}{2}$ minutes on 15th day.
Subacute case.	First clear fluid obtained on 15th day = Progressive increase in time occupied in global reaction from $\frac{3}{4}$ minute on 3rd day to $4\frac{1}{2}$ minutes on 15th day.
Subacute case.	First clear fluid obtained on 28th day = Progressive increase in time occupied by global reaction from $\frac{3}{4}$ minute on the 9th day to 3 minutes on 18th day.

TABLE XI

PERMANGANATE TESTS. THE GLOBAL TEST USED AS A TIME REACTION

One case detailed on successive days : illustrating the progressive increase in time reaction (time occupied in changing 1 c.c. of 0·01 per cent potassium permanganate solution mixed with 1 c.c. of cerebro-spinal fluid from pink to yellow).

Acute case received on the 2nd day of illness and recovering in 10 days

Day of Disease.	C.-s. Fluid Appearance.	Time Reaction.	Glucose Reaction.	Globulin test (Noguchi's).
2nd	Purulent	$\frac{1}{2}$ minute	Negative	+ +
3rd	,,	$\frac{3}{4}$,,	,,	+ +
4th	Turbid	1 ,,	Faint +	+ +
5th	,,	2 ,,	+	+
6th	Slightly turbid	$2\frac{1}{4}$,,	+	+
7th	,,	$2\frac{1}{4}$,,	+	+
8th	V. slightly turbid	3 ,,	+	+
9th	Trace of turbidity	$3\frac{1}{2}$,,	+	Sl. +
10th	Clear	5 ,,	+	Faint + after one hour

CYTOLOGY

The cellular constituents of normal cerebro-spinal fluid are extremely scanty and average about four cells per cubic millimetre (extremes 1 to 8 cells). The cells present are small lymphocytes, but an occasional endothelial cell may be met with. Polymorphonuclear leucocytes are not present under normal conditions. In all inflammatory conditions of the meninges, however, an increase in the cellular elements of the cerebro-spinal fluid takes place ; in pyogenic infections the polymorphonuclear leucocytes predominate, whereas in tuberculous meningitis the lymphocytes are usually in excess. In some cases of tuberculous meningitis exhibiting tubercle bacilli in the cerebro-spinal fluid which have come under our observation, the polymorphonuclear cells were more numerous than the mononuclear.

In meningococcal meningitis the cellular changes in the cerebrospinal fluid are characterised by the presence of polymorphonuclear cells which usually occur in large numbers. The number of the lymphocytes is also increased above the normal, but they are not nearly as numerous as the polymorph. cells. The lymphocytes present may be both large and small, and large degenerate endothelial cells are also frequently observed.

The absolute number of cells can be estimated by means of an ordinary haemocytometer pipette and counting chamber or by means of the more special Fuchs-Rosenthal apparatus ; such estimation, however, is of very little practical importance. The degree of turbidity or opalescence of the fluid and the amount of deposit on centrifugalisation are often useful indications of the severity of the meningitis, while a differential count of the cells in stained films is of considerable value. The number and character of the cells show some variation with the stage of the disease. During the premeningitic stage the cells in the cerebro-spinal fluid are unaltered in number and character. Two such cases came under our observation at this stage (Cases II. and III.) ; the cerebro-spinal fluid in both instances was perfectly clear and transparent, and showed no increase in cells and no organisms. The fluids obtained at the next lumbar puncture, 8-10 hours later, were both turbid and showed numerous polymorph. cells and a few mononuclears and meningococci. In the meningitic stage the cellular changes vary with the intensity and duration of the meningitis. In the earliest stage of involvement of the meninges the fluid may be perfectly clear and transparent.

At this period the organisms have reached the meninges, but have not been there sufficiently long for inflammatory reaction to manifest itself in the cerebro-spinal fluid. Four cases at this stage came under our observation. All showed some clinical evidence of meningitis. The fluids obtained on lumbar puncture of each, however, were quite clear, but meningococci were present in all : in three there was no abnormality in the cellular contents, while in the fourth an occasional polymorph. cell was seen. When the meninges have been involved for a slightly longer period, inflammatory reaction becomes well marked, and the polymorphonuclear is the predominant cell in the pus ; they are often present in enormous numbers. Mononuclear cells (lymphocytes), both large and small, are as a rule associated in varying numbers with the polymorph. cells, but are seldom present in nearly the same numbers. Occasionally a few large degenerate endothelial cells are also found.

In fulminating cases dying within 36 hours of the onset of illness, the cellular reaction in the cerebro-spinal fluid is often less marked than in acute cases running a slightly longer course. In all probability, as we have already pointed out (Chapter VII.), this is due to an overwhelming infection, more septicaemic than meningeal, and with deficient response on the part of the patient's system. Foster and Gaskell, Sophian, and others, state that occasionally in the cerebro-spinal fluid of fulminating cases lymphocytes may be present in equal numbers to the polymorph. cells, but this has not been our experience, the proportion of polymorphonuclears always having been the greater.

In acute cases recovering after a short course, the clinical improvement of the patient is associated with an absolute diminution in number of all the cells in the fluid. In subacute cases running a long course, the total number of cells usually diminishes in the later stages, but not infrequently this change is associated with an absolute increase in the number of mononuclears. In recrudescent cases an increase in the polymorphonuclears takes place with the recrudescence. In progressively purulent cases the number of cells become greater during the course ; but the polymorph. cells always constitute considerably the large proportion.

In general, with the exception of fulminating types, the more acute the case the greater is the predominance of polymorphonuclear cells in the fluid.

The cellular changes in the progress of a case are extremely interesting and are best studied in preparations stained by Leish-

man's method.   As has been pointed out in Chapter II., when dealing with the meningococcus and its allied organisms, the leucocytes found in the cerebro-spinal fluid at the first lumbar puncture in an established case, are usually degenerate, with poorly stained and disintegrated nuclei, the cytoplasm being broken down and the granules indistinct.   With improvement in the case, and as a result of reaction to intrathecal serum administration, fresh and more healthy leucocytes appear in the fluid, and can be recognised by their clearly staining well preserved nuclei and distinct cytoplasm granulations.   A few eosinophilic and basophilic leucocytes can frequently be made out in addition to the neutrophile polymorphs.   It seems probable that part of the therapeutic effect of the anti-meningococcal serum may be exercised by its stimulating production of fresh leucocytes and their consequent phagocytic action on the meningococci.

BACTERIOLOGY

The demonstration of the meningococcus in the cerebro-spinal fluid of a suspected case of cerebro-spinal fever is the only factor which confirms the diagnosis with absolute certainty.

During the pre-meningitic stage of the disease the organisms will not be found in the cerebro-spinal fluid, but may be cultivated from the blood ; it is seldom, however, that the cerebro-spinal fever is suspected at this stage.   When meningitis is definitely established the meningococcus can almost always be found in the cerebro-spinal fluid if sufficient care be taken.   Elser and Huntoon examining 210 cases found the organism in 92·5 per cent.   Of 23 cases, Sladen found it in all (100 per cent).   In a series of 36 consecutive cases examined by us during the winter of 1915–16 we demonstrated the organism in all but 2—97·2 per cent.   In a 1917 series of 37 cases, with improvement in technique, we found the meningococcus in all—100 per cent.

On no occasion have we observed pleomorphism of the meningococcus beyond the variation in size and staining affinity already described in Chapter II. (p. 6).

There exist several factors which may explain the occasional failure to find the meningococcus in the cerebro-spinal fluid of apparently definite clinical cases of cerebro-spinal fever.   In fulminating types the organisms may sometimes be very few in number, but this usually occurs only when the patient dies from the overwhelming intensity of a septicaemic process, within about 24 hours

of the onset. It is possible also that cases recovering very rapidly, in which the infection was slight and quickly overcome, may fail to exhibit meningococci unless sought for early in the course of illness. In chronic cases, during the later stages of the disease, the organisms are often extremely difficult to demonstrate ; when it is remembered that the chief seat of infection in such cases is at the base of the brain, causing thickening of the meninges and relative obstruction of the foramina of Magendie and Luschka, it is easily conceivable that meningococci may not escape into the spinal canal. Consequently, failure to find organisms in the cerebro-spinal fluid by no means indicates that infection of the meninges has ceased. In other cases, following the intrathecal administration of anti-meningococcal serum, no meningococci may be found in the fluid, nor is it possible to obtain a culture. A few cases may yield a growth of meningococci, but on direct examination of stained films no organisms can be seen ; more frequently, however, the diplo-cocci are seen but fail to grow in culture. In consequence of the action of the intracellular enzyme, the meningococcus tends to undergo more or less rapid disintegration ; this fact may render identification in films difficult and in culture doubtful. Also, as pointed out in Chapter II., the meningococcus is very sensitive to external influences and special media are necessary for its growth ; unless attention be paid to these important points the cultivation of the organism may be unsuccessful.

The technique which we have adopted in examining the cerebro-spinal fluid is as follows :

The cerebro-spinal fluid is brought without delay from the patient to the laboratory, being kept warm in transit. On receipt of the fluid its naked-eye appearances are noted and a portion centrifugalised ; by this means the cells and organisms are concentrated. Films and cultures are made at once from the centrifugalised deposit. A second portion of the fluid is kept in the incubator at 37° C. as not infrequently after 12-24 hours' incubation this fluid will show organisms, owing to the cocci having multiplied, when that examined without incubation has failed to do so. Two films are prepared, one being stained by Gram's method and the other with Leishman's stain ; the former differentiates the cocci and the latter the cells. For practical purposes the finding of definite Gram-negative diplococci on direct examination of the fluid in a case of meningitis is sufficient for a provisional diagnosis of cerebro-spinal fever. In the majority of cases the organisms are not difficult

to find, but in some a prolonged search is necessary in order to demonstrate even a few meningococci.

In general it may be said that the severity of meningitis corresponds roughly with the number of cocci present. The organisms may be intracellular or extracellular in varying proportions ; as a rule the presence of a large number of extracellular cocci is indicative of a severe form of the disease. The preparation of films from the cerebro-spinal fluid immediately after withdrawal is most important, as only then can a true idea of the number of organisms present and their relation to the cells be obtained. When the cerebro-spinal fluid is incubated prior to the preparation of the films, the extracellular organisms are increased in number and the cells themselves are usually more or less disintegrated. Owing to the action of the intracellular enzyme of the meningococcus, some of the cocci may even disappear from a fluid that has been left standing.

Cultures from the centrifugalised deposit are made on plates of " trypagar " to which blood suspension has been added, a liberal planting of the deposit being desirable. The plates are incubated at 37° C. and examined at the end of 24 hours, the examination being repeated if necessary after 48 hours. If no growth be obtained after 24 hours' incubation, a second plate may be inoculated from the incubated fluid. The appearance of the meningococcus colonies on this medium have already been described in Chapter II. (p. 11). When a sufficient growth has been obtained, subcultures are made on glucose serum agar and saccharose serum agar (litmus tinted), the remainder of the culture being submitted to macroscopic agglutination tests with specific sera.

The complete examination of the cerebro-spinal fluid every day that lumbar puncture is performed, is most important as a guide to prognosis and treatment. The disappearance of the organism and particularly its failure to grow in culture is of favourable significance, whereas persistence in culture is unfavourable. Clinically, the true significance of an elevation of temperature late in the course of the disease may only be discovered by finding that organisms have returned in the cerebro-spinal fluid, a recrudescence of the meningitis having taken place.

The Presence of Meningococci in the Cerebro-spinal Fluid in Relation to the Clinical Type of Case.—(1) *Fulminating Type.*— Meningococci are usually present in the cerebro-spinal fluid when definite meningitis is present. Although organisms may be present

in considerable numbers, in some cases they are scanty and entirely intracellular.

Of five fulminating cases, we found meningococci in the cerebro-spinal fluid of all ; in two they did not appear in culture.

(2) *Acute Fatal Cases.*—Meningococci are invariably found without difficulty in the first sample of cerebro-spinal fluid withdrawn ; extracellular forms often predominate. Also, as a rule they grow readily in culture. In the majority of cases the organisms are easily seen on direct examination of all fluids withdrawn by lumbar puncture, intracellular cocci often persisting until the day of death ; in some cases, however, after the first day or two they may fail to grow in culture.

The following table shows the results of bacteriological examination in 11 cases of the acute fatal type :

TABLE XII

ACUTE FATAL CASES (DEATH IN 4-7 DAYS). BACTERIOLOGICAL EXAMINATIONS

(Day = day of disease ; D = direct examination ; C = culture ;
+ = meningococci present ; – = meningococci absent)

Case.	1st Fluid.			2nd Fluid.			3rd Fluid.			4th Fluid.		
	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.
1	2nd	+	+	.	.	.	.	.	.	.	.	.
2	,,	+	+	.	.	.	.	.	.	.	.	.
3	,,	+	+	3rd	+	–	4th	–	–	.	.	.
4	,,	+	+	,,	+	–	,,	+	+	5th	+	+
5	,,	+	+	,,	+	–	,,	+	+	.	.	.
6	,,	+	+	,,	+	+	,,	+	+	5th	+	+
7	3rd	+	+	.	.	.	.	.	.	.	.	.
8	,,	+	+	5th	+	–	.	.	.	.	.	.
9	,,	+	+	4th	+	–	5th	+	–	6th	+	–
10	,,	+	–	6th	+	–	.	.	.	.	.	.
11	4th	+	+	.	.	.	.	.	.	.	.	.

(3) *Acute Cases recovering after a Short Course.*—Meningococci are almost invariably found in the first cerebro-spinal fluid withdrawn and are usually both extracellular and intracellular. In the majority of cases the organisms grow on culture. Fluids obtained during the succeeding few days usually show that the organisms have become greatly diminished in number and are almost exclusively intracellular ; also they not infrequently fail to grow. In some cases no meningococci are found after the first three or four days, while in others they persist until the ninth or tenth day.

The following table illustrates the bacteriological findings in 12 cases :

TABLE XIII

ACUTE CASES WHICH RECOVER AFTER A SHORT COURSE (8-14 DAYS).
BACTERIOLOGICAL EXAMINATIONS

(Day = day of disease ; D = direct examination ; C = culture ;
+ = meningococci present ; – = meningococci absent)

Case.	1st Fluid.			2nd Fluid.			3rd Fluid.			4th Fluid.			5th Fluid.			6th Fluid.		
	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.
1	1st	+	–	2nd	+	–	3rd	+	–	4th	+	–	5th	–	–	.	.	.
2	,,	+	+	3rd	+	+	5th	–	–	7th	+	–	9th	–	–	.	.	.
3	,,	+	–	2nd	+	–	3rd	+	–	4th	+	–	5th	+	–	6th	–	–
4	2nd	+	+	3rd	+	–	5th	–	–	.	.	.	.	.	.	.	.	.
5	,,	+	+	4th	–	–	9th	–	–	.	.	.	.	.	.	.	.	.
6	,,	–	+	3rd	+	–	4th	–	–	6th	–	–	.	.	.	.	.	.
7	,,	+	–	3rd	–	–	5th	–	–	6th	–	–	8th	–	–	.	.	.
8	,,	+	+	3rd	+	–	5th	+	–	7th	–	–	9th	–	–	.	.	.
9	,,	+	–	3rd	+	–	4th	+	–	5th	+	–	6th	+	–	8th	+	–
10	3rd	+	+	4th	–	–	5th	–	–	.	.	.	.	.	.	.	.	.
11	,,	+	+	4th	–	–	5th	+	–	6th	+	–	7th	+	–	9th	–	–
12	4th	+	+	5th	+	+	6th	+	+	7th	+	+	8th	+	–	9th	+	–

Cases 9 and 12 on the 9th and 11th day respectively were negative both on direct examination and culture.

(4) *Acute Cases running a Long and Severe Course.*—This type of case is comparatively rare ; organisms persist on direct examination, and usually also on culture, for often as long as thirty days before death occurs. The following are the bacteriological results in Case VI. (p. 84).

(Day = day of disease ; D = direct examination ; C = culture)

1st Fluid.			2nd Fluid.			3rd Fluid.			4th Fluid.			5th Fluid.			6th Fluid.		
Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day	D.	C.	Day.	D.	C.	Day.	D.	C.
2nd	+	+	4th	+	+	6th	+	+	11th	+	–	14th	+	+	18th	+	+

7th Fluid.			8th Fluid.			9th Fluid.			10th Fluid.			11th Fluid.		
Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.
20th	+	–	23rd	+	–	24th	+	+	26th	+	–	29th	+	+

(5) *Acute Cases becoming Subacute.*—Organisms are as a rule plentiful in the cerebro-spinal fluid during the early days of the course, and may often persist, although in diminished numbers, for about three weeks. Failure to obtain a growth on culture from the cerebro-spinal fluid while meningococci are still seen on direct examination of films is usually the first indication of diminished vitality of the cocci. Occasionally organisms may cease to be apparent in the cerebro-spinal fluid, yet the patient will show no sign of clinical improvement for many days.

The following table (3 cases) serves to illustrate the bacteriological results :

TABLE XIV

ACUTE CASES BECOMING SUBACUTE (3 CASES). BACTERIOLOGICAL
EXAMINATIONS

(Day = day of disease ; D = direct examination ; C = culture ;
+ = meningococci present ; – = meningococci absent)

Case.	1st Fluid.			2nd Fluid.			3rd Fluid.			4th Fluid.			5th Fluid.		
	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.
1	2nd	+	+	5th	+	+	7th	+	–	8th	+	+	10th	+	–
2	2nd	+	–	3rd	+	–	4th	+	–	6th	+	–	7th	–	–
3	2nd	+	+	3rd	+	+	4th	+	+	5th	+	–	7th	–	–

6th Fluid.			7th Fluid.			8th Fluid.			9th Fluid.			10th Fluid.			11th Fluid.		
Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.
12th	+	–	18th	+	–	24th	–	–	.	.	.	.	.	.	.	.	.
8th	+	–	9th	+	–	17th	+	–	18th	+	+	22nd	–	–	24th	.	.
9th	–	–	11th	–	–	14th	–	–	.	.	.	.	.	.	.	.	.

(6) *Abortive Types.*—The first sample of cerebro-spinal fluid withdrawn may show meningococci on direct examination, but frequently in culture no growth develops. In other cases no organisms are seen, but they appear in culture ; while in a few cases meningococci are not apparent in the cerebro-spinal fluid either on direct examination or in culture, but the naso-pharyngeal swab is positive. Organisms, if present, disappear after the second or third day of illness.

(7) *Progressively Purulent Types.*—The first fluid obtained

almost always reveals the presence of meningococci, which may be either intracellular or extracellular or both ; as a rule, a culture is not difficult to obtain. As the cerebro-spinal fluid becomes more and more purulent, meningococci almost invariably persist, not infrequently in diminishing numbers ; on the day of death the organisms may sometimes be absent from the sample of cerebro-spinal fluid withdrawn. In other cases the intracellular organisms tend to become more numerous. During the later stages meningococci are sometimes not obtainable in culture, but the tendency to disappear is not quite so frequent as in the acute fatal type.

The following table illustrates the bacteriological findings in six cases :

TABLE XV

PROGRESSIVELY PURULENT CASES. BACTERIOLOGICAL EXAMINATIONS

(Day = day of disease ; D = direct examination ; C = culture ;
+ = meningococci present ; − = meningococci absent)

Case.	1st Fluid.			2nd Fluid.			3rd Fluid.			4th Fluid.			5th Fluid.			6th Fluid.			7th Fluid.		
	Day	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.
1	2nd	+	+	3rd	+	−	4th	+	−	5th	+	+	6th	+	−	8th	+	+	.	.	.
2	3rd	+	+	4th	+	+	5th	+	+	.	.	.	.	.	.	.	.	.	.	.	.
3	3rd	+	+	5th	+	+	8th	−	−	.	.	.	.	.	.	.	.	.	.	.	.
4	3rd	+	+	4th	+	−	5th	+	+	6th	+	+	7th	+	+	8th	+	−	9th	−	−
5	4th	+	−	5th	+	+	6th	+	+	7th	+	+	8th	+	+	10th	+	−	.	.	.
6	4th	−	−	5th	+	−	7th	−	−	9th	+	+	10th	+	+	11th	+	+	13th	−	−

(8) *Recrudescent Types.*—In the majority of cases meningococci are easily identified in the early fluid withdrawn by lumbar puncture. After a variable interval they disappear from the cerebro-spinal fluid, such disappearance usually being heralded by failure to develop in culture. Then follows a period during which, if lumbar puncture be performed, no meningococci can be seen either on direct examination or obtained on culture from the cerebro-spinal fluid (*vide* Table XVI.) ; accompanying a recrudescence of meningeal symptoms, often after a considerable quiescent interval, organisms reappear in the cerebro-spinal fluid. This occurrence may be repeated several times (Table XVI. Case 4).

Table XVI. illustrates the results obtained in seven cases :

TABLE XVI

RECRUDESCENT CASES. BACTERIOLOGICAL EXAMINATIONS

(Day = day of disease; D = direct examination; C = culture;
+ = meningococci present; − = meningococci absent)

Case.	1st Fluid.			2nd Fluid.			3rd Fluid.			4th Fluid.			5th Fluid.		
	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.
1	2nd	+	+	3rd	+	−	5th	+	+	6th	+	−	7th	+	+
2	2nd	+	−	3rd	−	−	4th	+	−	5th	+	−	6th	−	−
3	4th	+	+	5th	+	−	6th	+	−	7th	−	−	8th	−	−
4	3rd	−	+	6th	+	−	12th	+	+	16th	+	−	20th	+	+
5	4th	+	+	5th	+	+	6th	+	−	7th	−	−	8th	−	−
6	6th	+	−	7th	−	−	8th	−	−	9th	−	−	10th	−	−
7	36th	+	−	37th	+	−	38th	+	−	39th	+	−	40th	+	−

Case.	6th Fluid.			7th Fluid.			8th Fluid.			9th Fluid.			10th Fluid.		
	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.
1	9th	+	−	10th	−	−	12th	−	−	13th	−	−	14th	←−	−
2	7th	−	−	8th	−	−	9th	+	−	10th	−	−	Recovered		
3	9th	+	−	10th	+	−	11th	+	−	12th	−	−	Recovered		
4	22nd	−	−	28th	−	−	33rd	−	−	35th	+	−	44th	−	−
5	9th	+	−	10th	−	−	15th	−	−	Recovered			.	.	.
6	.	.	.	(Recovered 11th day—recrudescent attack only represented; not seen during initial attack)											
7	41st	+	−	42nd	+	−	43rd	+	−	(Died 43rd day; recrudescent attack only represented)					

Case.	11th Fluid.			12th Fluid.			13th Fluid.		
	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.
1	Recovered			.	.	.	.	.	.
2	.	.	.	.	.	.	.	.	.
3	.	.	.	.	.	.	.	.	.
4	50th	−	+	55th	−	−	63rd	−	−
5	.	.	.	.	.	.	.	.	.
6	.	.	.	.	.	.	.	.	.
7	.	.	.	.	.	.	.	.	.

(9) *Subacute Cases (Mild).*—The organisms seen on direct examination are usually few in number and often they fail to grow in culture. The first fluid examined may occasionally show a few extracellular organisms, but the following day all are usually intracellular. Meningococci can seldom be found after the first few days of the course.

TABLE XVII

SUBACUTE CASES (MILD). BACTERIOLOGICAL EXAMINATIONS

(Day = day of disease ; D = direct examination ; C = culture ;
+ = meningococci present ; − = meningococci absent)

Case.	1st Fluid.			2nd Fluid.			3rd Fluid.			4th Fluid.		
	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.
1	3rd	+	−	4th	+	−	5th	−	−	6th	−	−
2	4th	+	+	5th	−	−	6th	−	−	7th	−	−
3	5th	+	+	6th	−	−	7th	−	−	.	.	.
4	3rd	+	−	7th	−	−	8th	−	−	.	.	.
5	2nd	+	−	8th	+	−	9th	−	−	.	.	.

(10) *Subacute Cases (Moderately Severe).*—(*a*) *Short Course (under 15 days).*—The first cerebro-spinal fluid examined usually shows a relatively small number of organisms ; intracellular forms usually predominate. Even if meningococci be cultivated from the first fluid it is seldom possible, following serum administration, to obtain them in culture from subsequent fluids. Any extracellular organisms rapidly become exclusively intracellular, scanty, and disappear towards the end of the first week of illness.

The following table illustrates the bacteriological findings in 10 of these cases :

TABLE XVIII

SUBACUTE CASES (MODERATELY SEVERE)—SHORT COURSE. BACTERIOLOGICAL EXAMINATIONS

(Day = day of disease ; D = direct examination ; C = culture ;
+ = meningococci present ; − = meningococci absent)

Case.	1st Fluid.			2nd Fluid.			3rd Fluid.			4th Fluid.			5th Fluid.			6th Fluid.		
	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.	Day.	D.	C.
1	2nd	+	−	3rd	−	−	4th	+	−	5th	−	−	.	.	.	.	.	.
2	2nd	+	−	3rd	+	−	4th	+	−	5th	−	−	.	.	.	.	.	.
3	2nd	+	−	3rd	+	−	5th	+	−	6th	−	−	7th	−	−	13th	−	−
4	3rd	+	+	5th	+	−	7th	−	−	.	.	.	.	.	.	.	.	.
5	3rd	+	+	4th	−	−	5th	−	−	.	.	.	.	.	.	.	.	.
6	3rd	+	−	4th	+	−	5th	+	−	6th	+	−	7th	−	−	8th	−	−
7	3rd	+	−	4th	−	−	5th	−	−	7th	−	−	8th	−	−	.	.	.
8	3rd	−	−	4th	+	−	5th	+	−	6th	−	−	7th	−	−	.	.	.
9	4th	+	−	5th	+	−	6th	+	−	7th	−	−	9th	−	−	.	.	.
10	9th	+	−	10th	+	−	12th	−	−	13th	−	−	.	.	.	.	.	.

(b) *Longer Course* (*over* 15 *days*).—These subacute cases often run a longer course than those mentioned above merely because they do not come under treatment until later in the disease.

The meningococci are found to be few in number, chiefly intracellular, and in culture, if indeed obtained, the growth is poor. At first not infrequently no organisms can be seen or cultivated, and it is not until the third or fourth lumbar puncture that the fluid yields a positive result. Under the influence of specific treatment the organisms gradually disappear.

(11) *Chronic Types*.—The bacteriological findings during the early stage of the course depend upon whether the case is primarily acute or subacute. The beginning of the chronic stage is often characterised by a gradual disappearance of the cocci, and the cerebro-spinal fluid may frequently be examined with negative results although clinically the patient remains in the same state. Intracellular meningococci may be seen on direct examination of films at intervals in some cases, while in others they may only appear on careful cultivation methods or after enriching the cerebro-spinal fluid by incubating for about 12 hours at 37° C. Not infrequently (*e.g.* in the posterior basic type of infants) the fluid obtained by intraventricular puncture will yield positive results when that withdrawn on lumbar puncture is apparently sterile.

The Relation of the Type of Meningococcus to the Type of Disease. —By the method of " absorption of agglutinins " Gordon, as already described in Chapter II. (p. 14), was able to differentiate the meningococci responsible for the outbreaks of cerebro-spinal fever in England from 1914 onwards into four definite strains or types based on their immunological characters. These he named Types I., II., III. and IV. respectively.

It occurred to us that there might be some difference in the virulence or pathogenic reactions of the four types of the coccus, in so far as the resulting disease is concerned, and the present section correlates the Type of Coccus with the Type of Disease.

Our observations are based upon a study of 43 cases of cerebro-spinal fever. In all except four the organism was cultivated from the cerebro-spinal fluid ; in three of these exceptions the coccus was seen on direct examination of the fluid, although it failed to grow on culture ; in each, however, a culture of the meningococcus was obtained from naso-pharyngeal swabs and the type of the organism thus determined. In the fourth, an abortive case, the organism was obtained from the naso-pharynx, but in the cerebro-

spinal fluid no meningococci were found on direct examination or culture.

(1) *Type I. Coccus.*—This type of meningococcus was found in ten cases. Without exception, all were severe, six proving fatal (mortality, 60 per cent). Of these, one was fulminating and died within 36 hours of the onset of illness. Three were of the progressively purulent type, *i.e.* the meningeal exudate becoming daily thicker and more purulent, two patients dying on the 9th and one on the 13th day of the disease. One was an acute fatal type, dying on the 4th day (Case XVI. p. 143). The last fatal case was a man, aged 60 years, who, although seriously ill, progressed favourably as regards his meningitis until the 8th day, when pneumonia of the right lower lobe unfortunately supervened. The lung condition apparently permitted a recrudescence of the meningitis, for organisms, absent on the 8th day, reappeared in the fluid on the 11th, the patient dying on the 16th day. The four cases that recovered were extremely severe but came under treatment early in the disease; one, nevertheless, ran a prolonged course of 40 days before he finally recovered. The other three patients were acutely ill, but recovered after courses of 10 days in two cases and 14 days in the last case.

All cases in this group were admitted to hospital in a delirious, stuporose or comatose condition. In seven the onset of the disease was sudden and abrupt; two had had a sore throat for about a week, but the actual onset of the cerebro-spinal fever was sudden. The remaining case showed a more gradual onset.

(2) *Type II. Coccus.*—In our experience this coccus was most frequently met with both in carriers and in actual cases; the types of disease associated with it are also most variable. Twenty cases were found infected with Type II. coccus; 14 recovered and 6 died (mortality, 30 per cent).

The types of disease found associated with this type were as follows:

Fulminating	.	.	.	.	0 ⎫
Acute fatal type	.	.	.	.	3 ⎬ fatal
Progressively purulent	.	.	.	3 ⎭
Acute cases recovering	.	.	.	4 ⎫
Abortive	.	.	.	.	1 ⎪
Recrudescent (severe)	.	.	.	3 ⎬ recovered
Recrudescent (moderate)	.	.	.	1 ⎪
Subacute (moderate)	.	.	.	4 ⎪
Subacute (mild)	.	.	.	1 ⎭
					20

Of the severe recrudescent cases, one ran a course of 80 days, another 24 and a third 22 days ; all eventually recovered. Two of the acute cases recovered after a course of six and seven days respectively ; the subacute cases of moderate severity exhibited courses varying from 7 to 22 days in duration.

A case of primary meningococcal septicaemia with ulcerative endocarditis but no meningitis (Case LIX. p. 347) also yielded on blood culture a Type II. meningococcus.

(3) *Type III. Coccus.*—This type was isolated in ten cases. Two cases occurred early in 1916 and the type was not met with again until December of the same year. Of the ten cases, six recovered and four died (mortality, 40 per cent). The following table shows the types of disease met with in association with Type III. coccus :

Fulminating	1	fatal
Acute fatal type	1	
Progressively purulent	0	
Early 1916 { Acute case long course (fatal)	1	
{ Subacute case becoming chronic	1	
Acute cases recovering after a short course	2	recovered
Acute case becoming subacute	1	
Recrudescent case (moderate)	1	
Subacute case (moderately severe)	1	
Subacute case (mild)	1	
	10	

(4) *Type IV. Coccus.*—One case only in which Type IV. coccus was obtained came under our observation. The patient was admitted to hospital during January 1917, and proved to be of the acute fatal type, dying within five days of the onset (Case V. p. 78).

One case occurring early in 1916, before an agglutinating serum for Type IV. coccus was obtainable, was found to be due to a meningococcus inagglutinable with any of the first three type sera. The patient recovered after a moderate course of 32 days, in spite of lobar pneumonia complicating the disease.

Atypical.—In one case only was an inagglutinable Gram-negative diplococcus with the cultural and fermentative reactions of the meningococcus obtained from the cerebro-spinal fluid. This was a subacute case of a mild character, occurring during January 1917 ; the patient recovered after a course of eight days.

From the above observations it will be seen that there is no

direct relationship between the type of organism and resulting type of disease. Type I., however, certainly gives rise to an infection of greater severity and is more resistant to treatment ; in the cases associated with this type terminating in recovery treatment in each instance was commenced early. In Type II. and Type III. cases the prognosis in general is more favourable.

SEROLOGICAL REACTIONS

Precipitins.—Vincent and Bellot described a specific precipitin reaction occurring in the cerebro-spinal fluid ; they considered that it could be used for the diagnosis of cerebro-spinal fever in cases in which the bacteriological examination was unsatisfactory. The test consists in adding 2-5 drops of anti-meningococcal serum to 50-100 drops of the clear supernatant part of the centrifugalised cerebro-spinal fluid and incubating the mixture at 37° C. for 6-10 hours. In positive cases the fluid tested shows a varying degree of cloudiness, while controls with normal serum remain quite clear. The test should be applied preferably to fluid withdrawn at the first lumbar puncture before any anti-meningococcal serum has been injected and as soon after withdrawal as possible. Occasionally the test only becomes positive after 24-36 hours' incubation.

The precipitin reaction is said to appear early in the course of the disease—within 12 hours—and to persist for 15-20 days. Vincent and Bellot state that they found the reaction negative in 61 normal subjects, while of 32 cases of meningococcal meningitis it was positive in all. In some cases Letulle and Legane found that the control became turbid spontaneously, thus rendering the test inconclusive ; in a few cases of pneumococcal meningitis a positive reaction was obtained. Bruynoghe in 1911 tested a series of cases, with the result that of 12 cases of cerebro-spinal fever, seven yielded a positive result and five a negative ; of 17 cases of illness other than cerebro-spinal fever, 16 were negative and one positive. The same observer also obtained a feebly positive reaction with the fluid from a case of poliomyelitis.

In 28 cases we attempted to demonstrate the presence of specific precipitins in the cerebro-spinal fluid. In each case the first sample of cerebro-spinal fluid withdrawn was examined, the test being carried out shortly after withdrawal. The method adopted was as follows :

The cerebro-spinal fluid is centrifugalised until the supernatant

portion is quite clear ; 1 c.c. of this clear fluid is then placed in each of 4 small test-tubes.   To each of these tubes 0·02 c.c. of Gordon's Type agglutinating serum is added, Type I. serum being placed in the first test-tube, Type II. in the second, Type III. in the third, and Type IV. in the fourth.   The resulting dilutions of serum are therefore 1 in 50.   Finally, the test-tubes are plugged with cotton-wool and incubated for 12-24 hours at 55° C.

12 fluids gave a positive result.   Of these :

3 showed a definitely cloudy precipitate with all four types of serum.
2 showed a slightly positive result with all four types of serum.
1 showed a well-marked positive result with Type I. serum only.
1 showed a slight positive result with Type 1 serum and a trace
     with Type II.
1 showed a definitely positive result with Type II. serum only.
1 showed a definitely positive result with Type II. serum and a
     slight positive with Type IV.
2 showed a slight positive result with Type II. only.
1 showed a slight positive result with Type IV. only.

All the fluids examined were found to contain meningococci, either on direct microscopical examination, on culture, or both.

Agglutinins.—Davis, in 1907, tested the cerebro-spinal fluid of meningitis patients for agglutinins ; the results were invariably negative, even in cases where the blood serum agglutinated in dilutions of 1 : 50 and sometimes higher.   In 1917, F. E. Taylor also obtained negative results in four cases tested.

Opsonins.—MacGregor, in 1906, examined the cerebro-spinal fluid for free opsonin, but found that it was absent from the cerebro-spinal fluid throughout the course of illness, no matter how high the opsonic index of the blood.   Mackenzie and Martin (1907) met with similar results.

Complement-fixation Bodies.—Weil and Kofke, in 1911, demonstrated that the cerebro-spinal fluid obtained from cases of meningococcal meningitis and added to guinea-pig's blood would give complete haemolysis.   Following this, Bruynoghe employed complement-fixation tests, using the sheep's blood haemolytic system, in a series of cerebro-spinal fluids obtained from patients suffering from cerebro-spinal fever.   To 1 c.c. of spinal fluid he added 1/20 c.c. complement and 1/100 c.c. of anti-meningococcal serum ; after incubation the corpuscles and amboceptor were added and the mixture incubated in the usual manner.   The result was positive in all of 12 cases of cerebro-spinal fever and negative in a series of fluids obtained from patients not suffering from meningitis.

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Positive reactions in the former appeared as early as the third day of illness.

Other Tests applied to the Cerebro-spinal Fluid.—*Sodium Taurocholate Test.*—Danielopolu found that the normal inhibition of cerebro-spinal fluid on the haemolytic action of sodium taurocholate on dog's blood is greatly increased in cerebro-spinal fever. He claims that this test is positive before there is any change in the cytology of the fluid (Heiman and Feldstein).

Animal Inoculation.—Von Grysez inoculated the lumbar subarachnoid space of small guinea-pigs with 0·5-0·75 c.c. of cerebro-spinal fluid from cases of cerebro-spinal fever ; death of the guinea-pig was thus produced in 2-24 hours. Von Grysez noticed, however, that within an interval of inoculation varying from 10 minutes to 24 hours the guinea-pig exhibited a reduction of temperature of 4°-8° C. ; he considered this lowering of temperature characteristic, and advocated the employment of this test in the case of cerebro-spinal fluids revealing no meningococci. Normal fluids and fluids from cases of tuberculous meningitis and cerebro-spinal syphilis were used as controls and yielded negative results.

CHAPTER XI

THE BLOOD

BLOOD PRESSURE

THE first important series of clinical investigations on the variation in blood pressure at different stages of meningitis were made by Robinson in 1910. This observer also attempted to determine the possible relationship existing between the degree of intracranial pressure and the blood pressure and particularly the effect upon the latter of removing cerebro-spinal fluid by lumbar puncture. Sophian also, in 1913, carried out similar observations, describing in addition the effect produced on the blood pressure by the intrathecal injection of serum. In 1915, Fairley and Stewart, in Australia, repeated the investigation in a large number of cases of cerebro-spinal fever.

The Blood Pressure at different Stages of the Disease.—(1) *At Onset*.—Since cerebro-spinal fever is seldom diagnosed during the premeningitic stage, most records of blood pressure relate to the earlier stages of meningitis. In mild cases and those of only moderate severity the blood pressure is but little altered ; in fulminating and very acute types, however, especially when a purpuric rash is present, the pressure is usually much diminished, not infrequently being too low to record. Fulminating cases usually exhibit a subnormal temperature and die without any reactionary rise in blood pressure. Other acute cases may present no very marked signs of toxaemia beyond the low blood pressure ; after the first day or two the latter may show a considerable rise, the patient, however, remaining severely ill and often dying within 6-7 days.

Of 26 patients examined on the first or second day of illness, Fairley and Stewart found that 19 exhibited a blood pressure of

under 120 mm. mercury; in the remaining 7 the pressure was above this level. Of the former class 17 died, but of the latter 1 only proved fatal. From these observations it follows that the presence of a low blood pressure during the first two days of illness, whether symptoms of collapse be present or not, is a prognostic sign of grave import—a view which we are able fully to endorse.

The following graphs (Figs. 34 and 35) of blood pressure
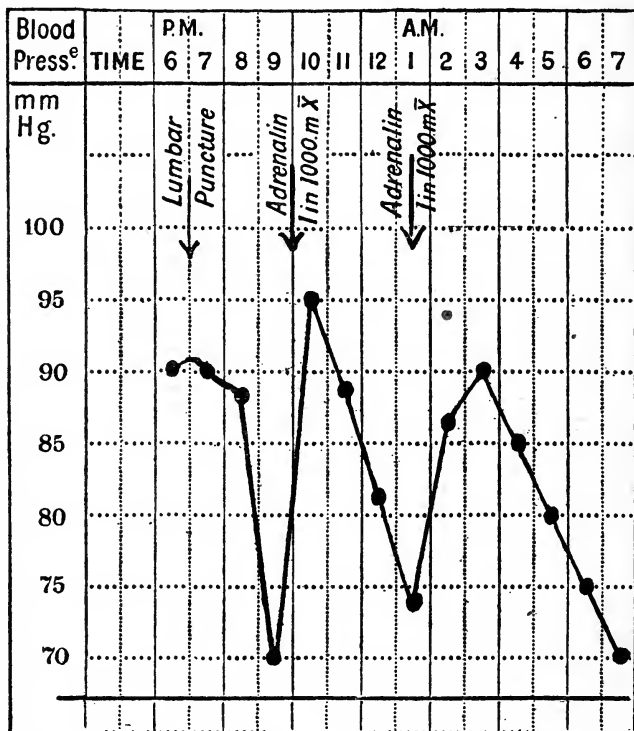
FIG. 34.—The blood pressure in a fulminating case with a purpuric rash and yielding a positive blood culture, dying on the 2nd day of illness within 14 hours of admission to hospital. The transient effect of adrenalin solution (10 minims, 1 in 1000) administered intravenously is well shown. Rectal salines were not retained.

registrations taken at hourly intervals in two fulminating cases coming under our observation serve to illustrate the low pressure observed in patients suffering from profound toxaemia. The transitory and comparative effects of adrenalin given intravenously and saline solution administered per rectum are also well shown.

(2) *During the Course of Meningitis.*—Robinson noted that in

many of his cases the blood pressure was distinctly raised during the course of the disease, the highest readings frequently being associated with the more serious symptoms of meningitis. Sophian states that in the majority of cases the blood pressure exceeds normal. Our experiences, however, coincide with those of Fairley and Stewart, viz. that if blood pressure readings be taken in every type of case continuously throughout the course of illness, the
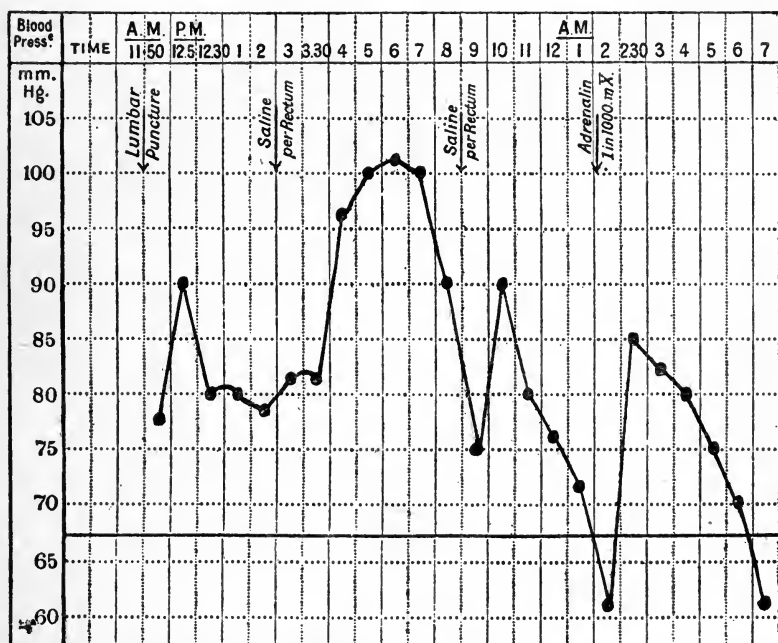
FIG. 35.—The blood pressure in a fulminating case with a purpuric rash, etc. The comparative effects of adrenalin administered intravenously and saline solution administered rectally are illustrated.

greater number exhibit an average blood pressure below 120 mm. of mercury.

The average state of the blood pressure is of some value in estimating prognosis. Of 242 cases, Fairley and Stewart found that subsequent to the third day of illness the average blood pressure was above 120 mm. of mercury in 116, and below this figure in 126. Of the latter group 99 cases recovered and 27 died (mortality, 21 per cent), while of the 116 patients with a blood pressure higher than 120 mm. of mercury no less than 81 died (mortality, 70 per cent).

As both the blood pressure and the mortality rate increase with age, some allowance must be made for this factor. Nevertheless, at all ages, it still appears that cases with a continued average blood pressure of over 120 mm. are uniformly more fatal than those in which the average blood pressure is below this level.

With these conclusions we are in entire agreement, having experienced similar results in our own cases; the fact that a case
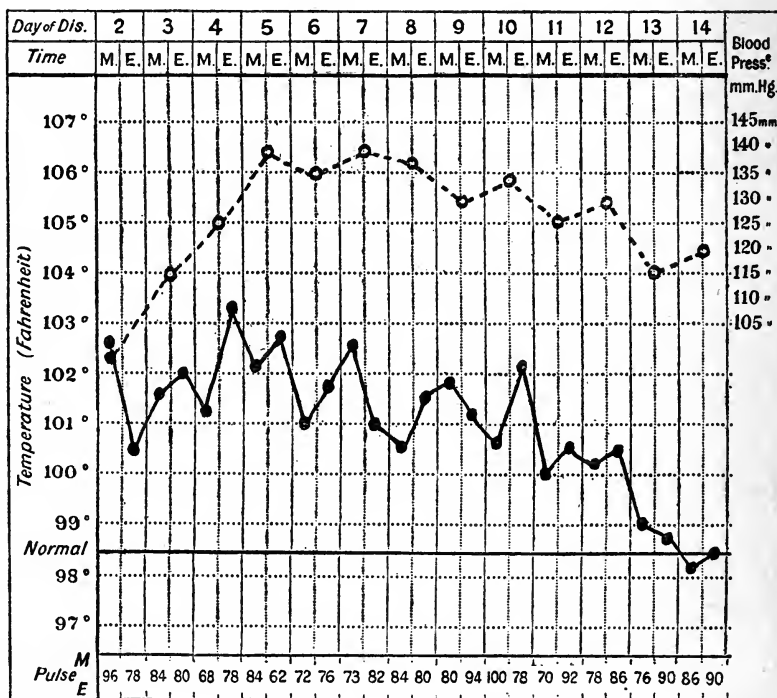
FIG. 36.—The blood pressure in an acute case. On the 14th day of illness the cerebro-spinal fluid was quite clear to the naked eye and sterile. The average daily blood pressure has been arrived at from the average of the 4-hourly readings in each 24 hours.

in the early stage of meningitis may exhibit a slightly raised or normal blood pressure in no way modifies the statement that a subsequent high blood pressure is of grave prognostic significance. Also, mention has already been made (Chapter IV. p. 48) of the high mortality rate occurring in cases of cerebro-spinal fever associated with vasculo-renal disease—one of the chief pathological causes of high blood pressure.

As rapid variations in the blood pressure readings may occur from time to time, even within 24 hours, it is necessary for purposes of comparison to take the average blood pressure over a period of at least seven days. In cases exhibiting severe meningitic symptoms the blood pressure may reach a considerable height (*e.g.* 180-190 mm. Hg.). As a consequence of this increased intravascular tension in elderly patients cerebral haemorrhage may occur. In children an increased blood pressure is also frequently found; Sophian mentions that in cases below the age of ten years he has sometimes found a blood pressure as high as that in adults. In children of about one year a reading of 90-100 mm. is not uncommon. Towards recovery severe cases usually exhibit a moderate fall in blood pressure (Fig. 36), and with the subsidence of symptoms it almost invariably reaches the normal level. During the coma that precedes death, owing to the failure of the general circulation, the blood pressure curve shows a rapid fall.

The fluid intake being constant, Fairley and Stewart were unable to establish any relationship between the degree of blood pressure and the quantity of urine excreted.

Blood Pressure in Recrudescent Cases. — A recrudescence of meningitic symptoms following an interval of improvement is frequently but by no means constantly preceded or accompanied by a rise of blood pressure. Owing to the pressure variations which may occur at all stages of the disease, however, it is impossible to predict a recrudescence by such a rise in tension. Fig. 37 illustrates the rise in blood pressure accompanying a recrudescence in a moderately severe case; the patient eventually recovered.

One of the effects of all severe bacterial infections is to produce a general fall in blood pressure; a similar lowering is seen in pneumonia, typhoid and all acute bacteriaemic processes. Maclagan and Cooke suggested that in cases of the fulminating type of cerebrospinal fever the greatly diminished fall and later absence of blood pressure, together with the general muscular flaccidity, could be accounted for by the haemorrhagic state of the adrenal bodies, not infrequently found at autopsy in these cases. The destruction of adrenal glandular tissue would, they consider, lead to a loss of epinephrin, the normal stimulus of the " myoneural function." As we have pointed out above, however, all severe bacterial infec-

tions are accompanied by a diminished blood pressure, the low degree of which is a clinical indication of the severity of the process. Also, we have shown elsewhere (p. 137) that there is some reason for believing that the fulminating type of cerebro-spinal fever is constituted by a severe blood infection by the meningococcus. These facts would amply account for the low blood pressure and muscular flaccidity so constantly observed in these cases. Further,

Day of Dis.	4th		5th		6th		7th		8th		9th		10th		11th		12th		13th		14th		15th		Blood Press.
Time	M.	E.	M.	E.	M.	E.	M.	E.	M.	E.	M.	E.	M.	E.	M.	E.	M.	E.	M.	E.	M.	E.	M.	E.	mm.Hg.
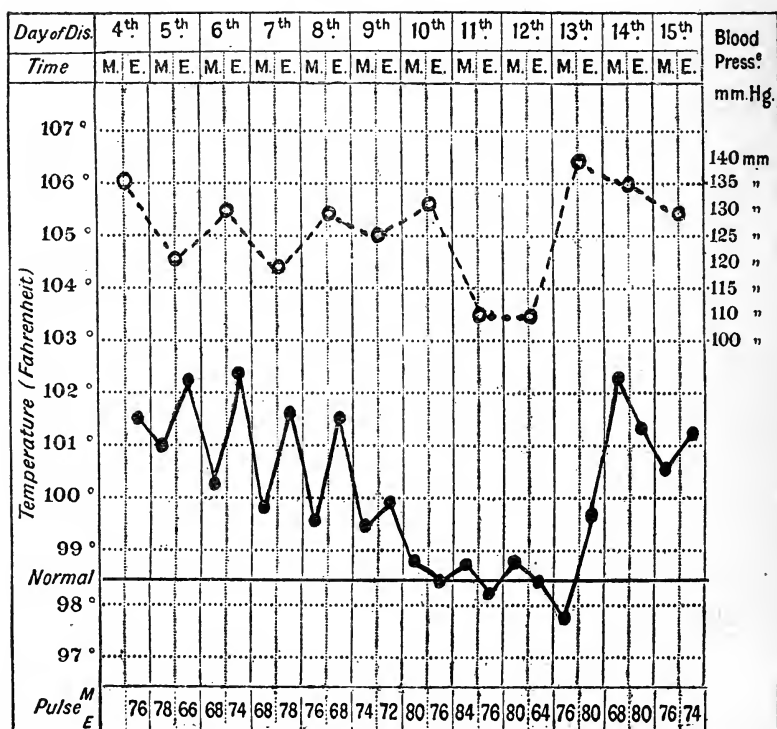
FIG. 37.—The blood pressure in a moderately severe case exhibiting a decline of symptoms on the 9th day and apyrexia for 3 days, followed by a recrudescence on the 14th day. The chart illustrates the rise in average blood pressure accompanying the recrudescence and is shown in relation to the temperature and pulse rate.

we have found haemorrhagic adrenalitis is by no means always present at autopsy in fulminating types, while clinically diminished blood pressure and muscular flaccidity are invariable symptoms. With the general failure of circulation in all conditions proving rapidly fatal the blood pressure soon reaches a level too low to permit of its being recorded. Cerebro-spinal fever differs from

most bacterial infections, however, in that subsequent to the onset the blood pressure, instead of remaining low, tends to rise in those cases exhibiting the more severe meningitis.

Harvey Cushing, in 1901, showed experimentally that when the intrathecal tension is raised by means of saline solution introduced into the subarachnoid space, the blood pressure rises. He concluded, therefore, that an increase in intracranial tension produces a rise in blood pressure, the latter tending to find a level slightly above that of the pressure exerted against the medulla. This is brought about, it was considered, by the action of a vaso-motor regulatory centre situated in the medulla, and which is stimulated by the rise in intracranial pressure.

In order to prove the hypothesis clinically in meningitis, it is necessary that the degree of intracranial pressure be determined. The methods available for this estimation of the intracranial pressure would appear to be as follows :

(1) *The Quantity of Cerebro-spinal Fluid evacuated on Lumbar Puncture.*—It soon becomes apparent that there is no constant relationship existing between the quantity of cerebro-spinal fluid obtainable by lumbar puncture and the degree of existing intracranial pressure. Often a considerable amount of fluid (40-60 c.c.) may be obtained only after several minutes, the fluid escaping from the needle drop by drop ; at other times, although a much smaller quantity of fluid escapes, the initial flow may appear as a forcible jet the moment the theca is penetrated. Further, no definite relationship can be established between the degree of blood pressure and the quantity of cerebro-spinal fluid evacuated. On further inquiry the reason for these facts becomes obvious. In adults, the capacity of the cranial cavity being fixed, not only does the accumulation of fluid in the ventricles and subarachnoid space tend to increase intracranial pressure, but also other conditions such as general cerebral congestion and dilatation of the blood vessels, accumulation of exudate, and oedema of the brain tissue itself. No true index of intracranial pressure can be determined without taking these factors into account.

(2) *The Quincke Manometer.*—This instrument is described on p. 234 ; with its use the intrathecal pressure existing at the point of lumbar puncture may be measured. Observations were made by Fairley and Stewart in several cases with a view to determining the ratio existing between the intracranial pressure, as measured by the Quincke manometer and the blood pressure.

These authors were, however, unable to arrive at any definite conclusion. Their observations showed that :

(a) Although increased intrathecal pressure was a concomitant of high blood pressure, it was also present in cases exhibiting a low blood pressure.

(b) In the average case with a high blood pressure no relationship could be demonstrated between the intrathecal pressure and the blood pressure ; e.g. a case one day showing a blood pressure of 140 mm. Hg. and an intrathecal pressure of 400 mm. water, might on the following day register a blood pressure of 160 mm. Hg. and intrathecal pressure of 300 mm. water.

The possible explanations of this failure to correlate the blood pressure and the intrathecal pressure are :

(1) The intrathecal pressure as indicated by the Quincke manometer is not a correct measurement of intracranial pressure or of the pressure in the region of the medulla. In reality the Quincke manometer measures only the intrathecal pressure existing in the subarachnoid space at the point where lumbar puncture is performed, and since the subarachnoid space is not continuous but is interrupted by numerous septa or trabeculae, the pressure existing at one point may not correspond to that existing at another.

(2) The reactive mechanism described by Harvey Cushing for an experimentally induced augmentation of intracranial pressure may not be called into play in such a pathological condition as meningitis, in which the development of increased intracranial pressure is only very gradual. Further, it must be remembered that although Cushing found, as Fairley and Stewart point out, that when the intracranial tension was raised by salt solution forced into the subarachnoid space the blood pressure rose, he also demonstrated that this regulatory mechanism was only called into activity when the extravascular pressure (intracranial tension) tended to rise above the intravascular pressure (arterial pressure). This mechanism enables the blood pressure to remain at a point just sufficient to prevent the persistence of anaemia of the medulla.

(3) Robinson also pointed out that if a pressure existed in the subarachnoid space in man corresponding to the systemic arterial blood pressure (which in the dog is 150 mm. Hg.), the intrathecal pressure in meningitis should be very much higher than is indicated by a manometer attached to a lumbar puncture needle. Consequently, it is possible that the intracranial pressure in the average

case of meningitis may not reach a level sufficiently high to stimulate the blood-pressure regulating centre.

Other theories advanced to account for the frequent high blood pressure in meningitis are summarised by Robinson as follows :

(a) Active muscular movements associated with delirium.

(b) Fever.

(c) Reflex stimulation of the blood-pressure raising mechanism by irritation of the central nervous system, or less directly by means of pain.

(d) Irritative phenomena analogous to the slow vagus pulse, photophobia and delirium, seen in meningitis.

(e) Reflex peripheral sensory stimulation, especially of the posterior spinal nerve-roots.

No experimental evidence, however, has been produced in support of any of the above explanations.

It was thought by Fairley and Stewart that possibly a condition of hyperpituitarism might exist to account for the increased blood pressure. This was suspected on account of the comparative frequency of perihypophyseal inflammation found in cases of cerebro-spinal fever, and also that the gland, at autopsy, sometimes appeared congested and swollen ; the increased vascularity induced by inflammation, it was considered, would lead to augmented glandular function. It is well known that the pars intermedia of the pituitary gland secretes one or more hormones which possess the power of maintaining the blood pressure ; such a hormone, if secreted in excess, would occasion a continued rise in blood pressure. Further, it is a physiological fact that the pituitary gland exercises some control over the metabolism of carbohydrates ; in hyperpituitarism the capacity for assimilating glucose is diminished and in hypopituitarism increased.

In testing this theory, therefore, a series of pituitary glands were dissected out at autopsy on cases of cerebro-spinal fever and microscopically examined. No changes sufficiently characteristic, however, were found to differentiate the changes from those occurring in the gland during other febrile conditions. The power of assimilating carbohydrates was also tested in a number of cases by administering test amounts of glucose (150 grms.) and examining 24-hourly specimens of urine. Had hyperpituitarism been present, it would be expected that glucose would appear in the urine within 24 hours. The results, however, were negative, as in several cases with a blood pressure over 125 mm. Hg. no

glucose whatever appeared in the urine, while in four cases with a blood pressure below 125 mm. Hg. sugar appeared in the urine in from 4 to 8 hours. Consequently, it does not appear that the increased blood pressure in meningitis is dependent upon a condition of hyperpituitarism.

The Blood Pressure in Internal Hydrocephalus.—When internal hydrocephalus develops the blood pressure frequently rises and in some cases may be relatively higher than that observed during the course of severe meningitis. Fairley and Stewart in 25 cases of internal hydrocephalus found the blood pressure definitely raised in 24 (96 per cent). In very chronic cases, however, as, for instance, in the posterior basic type of infants, a low blood pressure is not infrequently recorded.

In internal hydrocephalus, both clinical observations and post-mortem findings are usually in accord with the experimental work of Harvey Cushing. The fluid accumulated in the ventricles, including the fourth ventricle, is under considerable tension, as shown by the condition of dilatation of these cavities so constantly found at autopsy. The pressure exerted in the fourth ventricle stimulates the vaso-motor regulatory centre, and as the blood pressure always tends to reach a level slightly above that of the pressure exerted against the medulla, the former must of necessity rise.

To account for the low blood pressures sometimes observed in very chronic cases of the disease, Sophian suggests that owing to exhaustion from prolonged over-stimulation the vaso-motor centre may be unable to produce a sufficient reactionary rise in blood pressure.

The Effect on Blood Pressure of the Withdrawal of Cerebro-spinal Fluid from the Subarachnoid Space.—Robinson found that the changes in blood pressure occurring on the removal of cerebro-spinal fluid by lumbar puncture were by no means constant; of 39 cases 23 exhibited a slight fall in blood pressure; in 11 a slight rise was apparent, while in five no change whatever was noted. Similarly, Fairley and Stewart in 119 cases found that 46 (38·6 per cent) showed a fall in blood pressure of more than 4 mm. Hg. on removing cerebro-spinal fluid by lumbar puncture, 44 (37 per cent) exhibited a rise exceeding 4 mm. Hg., and in the remaining 29 (24·4 per cent) the change noted did not vary within 4 mm. Hg. from the blood pressure reading taken before lumbar puncture was performed. It is clear, therefore, that the effect on the blood

pressure of withdrawing cerebro-spinal fluid is most irregular ; indeed, we found that in the same case of cerebro-spinal fever, on the removal of approximately equal amounts of fluid, a fall in blood pressure may be exhibited one day, a rise the next, and no change the third day. Whether a fall or a rise be observed, its range seldom exceeds 10 mm. Hg.

Although it is not possible to foretell the effect on blood pressure of lumbar puncture, it would seem that cases exhibiting a blood pressure of below 120 mm. Hg. are more prone to exhibit a rise, while in the majority of those with a pressure above this figure a fall occurs on the removal of cerebro-spinal fluid. Thus, Fairley and Stewart found that in 40 cases with an initial blood pressure below 120 mm. Hg., on lumbar puncture a rise of over 4 mm. occurred in 29 (72 per cent). There is no apparent relationship between the stage of the disease at which the withdrawal of cerebro-spinal fluid is performed and its effect on blood pressure.

The actual quantity of cerebro-spinal fluid withdrawn is without apparent influence on the blood pressure reading. We have at times withdrawn as much as 100 c.c. of cerebro-spinal fluid at one puncture and noted no change in blood pressure. In some cases with a comparatively low initial blood pressure no change may be noted until over 40 c.c. are withdrawn, as in the example shown in Fig. 38.

Sophian states that the blood pressure frequently drops if the cerebro-spinal fluid is allowed to run out as rapidly as possible through the lumbar puncture needle. This observation we have not been able to confirm, the cases examined exhibiting little or no change ; one result, however, of allowing the fluid to escape too rapidly is that the patient complains of severe headache.

The tapping of the ventricles by direct puncture, according to Sophian, causes little or no change in blood pressure.

The Effect on Blood Pressure of the Intrathecal Injection of Serum.—The usual effect of the intrathecal administration of therapeutic serum is to produce a fall in blood pressure, and it is relatively few cases that exhibit either no change or a rise. The fall, indeed, is so constant that Sophian considered that blood pressure observations should invariably be made during intrathecal injections of serum, as by such means was afforded the most reliable information regarding the amount of serum that could be safely introduced. If, however, the gravitation method be used and the serum allowed only slowly to run in, the procedure is perfectly

safe and the registration of blood pressure unnecessary; in many hundreds of injections we have experienced no untoward results.

Irrespective of any previous change in blood pressure that may have occurred on the removal of cerebro-spinal fluid from the intrathecal sac, Sophian found that injecting even a moderate quantity of serum (*e.g.* over 4 c.c. in children and over 8 c.c. in adults) caused a drop in blood pressure, with a steadily increasing fall as larger quantities were introduced. These results we were able fully to confirm, and Figs. 38 and 39 serve to illustrate the fall in blood pressure that occurs during the intrathecal adminis-

Blood presse mm.Hg.	Initial Blood presse.	No. of c.c. of c·s fluid withdrawn						3 minutes after l.p	No. of c.c. of Serum administered						2 mins. later	10 mins. later
		10	20	30	40	50	60		5	10	15	20	25	30		
130																
120																
110																
105																
100																

Fig. 38.—Chart illustrating the effect on blood pressure of withdrawing cerebro-spinal fluid by lumbar puncture and subsequently injecting anti-meningococcal serum.

tration of serum; the blood pressure was registered at intervals according to the quantity of serum introduced.

The degree of blood pressure, whether high or low, existing prior to the administration of serum, appeared to exert no influence on the subsequent fall; consequently the initial blood pressure was no indication as to the extent of the diminution to be expected. In cases, however, where a considerable amount of cerebro-spinal fluid has been removed with little or no change in blood pressure, one may frequently introduce serum in quantities up to 30 c.c. and 40 c.c. with only a moderate fall. Injecting larger quantities of serum than fluid removed usually produces a very considerable lowering of blood pressure, and may be followed by symptoms of collapse with respiratory failure; exceptions in which may be

administered a somewhat larger quantity of serum than of cerebro-spinal fluid evacuated are mentioned on p. 421.

Similarly the pressure used and the rapidity with which the serum is injected are of the utmost importance. Even small quantities of serum administered under high pressure, *e.g.* with a syringe, or run in very quickly by gravity produce a more sudden and profound fall in blood pressure than larger quantities of serum run in slowly and under low pressure ; 5-10 minutes should be occupied in administering 30 c.c.

The time occupied by the blood pressure in regaining its previous level after the depression occurring during serum administration
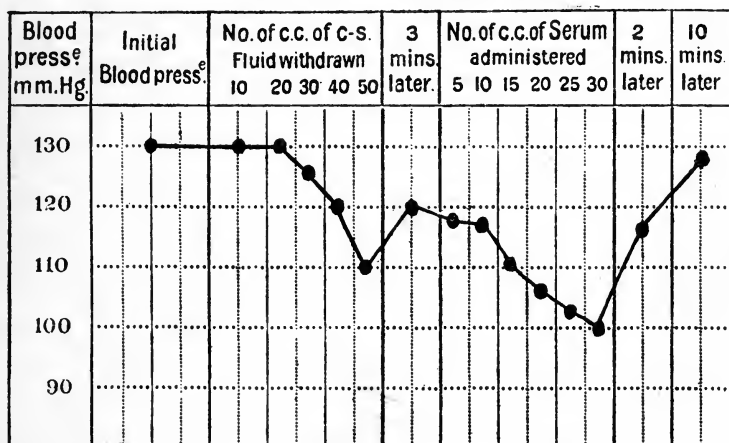
FIG. 39.—Chart illustrating the effect on blood pressure of withdrawing cerebro-spinal fluid by lumbar puncture and subsequently injecting anti-meningococcal serum.

is usually short. Often within a few minutes of the cessation of serum injection the blood pressure will be found to have risen a few mm., and 5-10 minutes later will have reached its previous level. According to Sophian, when there has been a large drop with symptoms of shock, the tendency of the blood pressure is to continue dropping even after the cessation of the inflow of serum.

In Sophian's series of cases less than 2 per cent showed a persistent rise of blood pressure during the intrathecal administration of serum. Some cases may exhibit a temporary rise on injecting a few c.c., followed by the usual fall. The direct introduction of serum into the ventricles appears to cause less change than injection by the spinal route.

The increase in intracranial tension produced by all injections

of serum differs markedly from the usual pathological increase of intracranial pressure that occurs in meningitis ; the latter develops only slowly and occupies at least a period varying from several hours to several days to accumulate. This would allow, if the vaso-motor regulating centre is brought into action, a gradual accommodation in blood pressure. During the intrathecal injection of serum there occurs a rapid increase in intracranial pressure within a few minutes. It is possible, therefore, that such excessive stimulation of the vaso-motor regulating centre leads to its exhaustion, thus causing a rapid fall in blood pressure which increases with the quantity of fluid injected. This explanation, as Sophian points out, would account for the fall in blood pressure that occurs on injecting serum as being due to the immediate mechanical effect. The tendency to regain the loss in blood pressure and return to that level existing before the injection, which, as we have shown, frequently takes place within a few minutes of the termination of serum administration in those cases exhibiting only a moderate fall, together with the tendency to further fall in those in which a very large drop occurs, appears to furnish further evidence in support of this explanation.

It has been demonstrated by different observers that when serum is injected into the general circulation of animals there frequently occurs a large drop in blood pressure. This chemical factor in serum has also, therefore, to be considered as a possible explanation for the fall in blood pressure following the intraspinal injection of serum.

CYTOLOGY OF THE BLOOD

A well-marked leucocytosis is a constant feature in cerebrospinal fever during the acute stages, and also usually in subacute and chronic cases. The leucocytosis, which often varies in degree from day to day, depends upon a relative increase in the polymorphonuclear cells. Sladen, from 21 cases of cerebro-spinal fever in whom repeated blood counts were carried out, concluded that the degree of leucocytosis did not appear to exhibit any constant relation to age, severity, or day of disease, excepting as an indication of the resistance of the individual concerned. Dow, as the result of blood examinations in a large number of cases, found that while the great majority, both children and adults, exhibited an increase in the polymorphonuclear cells, a lympho-

cytosis may be very occasionally observed in infants and young children.

In 31 of our cases we carried out systematic leucocyte counts ; in the majority the cells were estimated daily throughout the course of the disease from the time the patient first came under observation.

The first count in each case was performed either on the day of admission to hospital or on the day following ; the results obtained in the 31 cases are shown in the following table :

TABLE XIX

LEUCOCYTOSIS (31 CASES)

Leucocyte Counts.	No. of Cases.	Percentage.
Under 10,000 per c.mm.	0	0
10,000–15,000 ,,	8	25·8
15,000–20,000 ,,	5	16·13
Over 20,000 ,,	18	58·06

It is thus apparent that the disease is accompanied by a leucocytosis, and that in more than half the cases (58 per cent) the white cells number over 20,000 per c.mm. In the remaining cases the leucocyte count varies from 10,000 to 20,000.

Differential Leucocyte Counts.—Differential leucocyte counts were made in 13 of the cases ; in all it was evident that the leucocytosis was due to an increase in the neutrophile polymorphonuclear cells. The highest neutrophile count (93 per cent) was found on the third day of illness in an acute case, the total leucocyte count being 45,000 per c.mm. ; the patient recovered after a short course of nine days. The differential leucocyte count was as follows :

Neutrophile polymorphs . . . 93 per cent.
Eosinophiles . . . . . 0 ,,
Basophiles . . . . . 0 ,,
Lymphocytes (small) . . . . 2 ,,
Lymphocytes (large) . . . . 3 ,,
Large hyaline cells . . . . 1 ,,
Transitional cells . . . . 1 ,,

On the following day (4th day of disease) the leucocyte count was 18,200 and showed the following differential count :

Neutrophile polymorphs . . . 82 per cent.
Eosinophiles . . . . . 1 ,,
Basophiles . . . . . 0 ,,

Lymphocytes (small)	8 per cent.
Lymphocytes (large)	4 ,,
Large hyaline cells	3 ,,
Transitional cells	2 ,,

On the following day (5th day of disease) the patient showed 20,200 leucocytes and a differential count as shown below :

Neutrophile polymorphs	83 per cent.
Eosinophiles	5 ,,
Basophiles	5 ,,
Lymphocytes (small)	6·5 ,,
Lymphocytes (large)	4 ,,
Large hyaline cells	3 ,,
Transitional cells	2·5 ,,

Three days later this patient's leucocyte count had fallen to 7000, and the differential count was as follows :

Neutrophile polymorphs	71 per cent.
Eosinophiles	0 ,,
Basophiles	1 ,,
Lymphocytes (small)	14 ,,
Lymphocytes (large)	9 ,,
Large hyaline cells	3 ,,
Transitional cells	2 ,,

The cerebro-spinal fluid in this case was almost clear at this date ; on the day following it was perfectly clear and transparent.

An *acute fatal case*, dying on the seventh day of illness, showed on the second day 19,600 leucocytes per c.mm., with the following differential count :

Neutrophile polymorphs	87 per cent.
Eosinophiles	1 ,,
Basophiles	0 ,,
Lymphocytes (small)	2 ,,
Lymphocytes (large)	3 ,,
Large hyaline cells	4 ,,
Transitional cells	3 ,,

A *progressively purulent case*, dying on the tenth day of disease, exhibited on the ninth day 23,800 leucocytes per c.mm. ; the differential count is tabulated below :

Neutrophile polymorphs	89·5 per cent.
Eosinophiles	0 ,,
Basophiles	0·5 ,,
Lymphocytes (small)	4 ,,
Lymphocytes (large)	3 ,,
Large hyaline cells	1·5 ,,
Transitional cells	2·5 ,,

A *recrudescent case* (non-fatal) showed the following differential counts :

Day of Disease.	Total Leucocytes,	Differential Leucocyte Count.		
3rd	24,600	Neutrophile polymorphs	.	84·4 per cent
		Eosinophiles . .	.	0·4 ,,
		Basophiles	.	0 ,,
		Lymphocytes (small) .	.	4·4 ,,
		Lymphocytes (large) .	.	4·8 ,,
		Large hyaline cells .	.	3·6 ,,
		Transitional cells . .	.	2·4 ,,
4th	19,400	Neutrophile polymorphs	.	78 per cent
		Eosinophiles . .	.	1 ,,
		Basophiles . .	.	0·5 ,,
		Lymphocytes (small) .	.	8·5 ,,
		Lymphocytes (large) .	.	5·0 ,,
		Large hyaline cells .	.	4·5 ,,
		Transitional cells . .	.	2·5 ,,
5th	12,600	Neutrophile polymorphs	.	76 per cent
		Eosinophiles . .	.	0 ,,
		Basophiles . .	.	1 ,,
		Lymphocytes (small) .	.	10 ,,
		Lymphocytes (large) .	.	8 ,,
		Large hyaline cells .	.	3 ,,
		Transitional cells . .	.	2 ,,
6th	15,400	Neutrophile polymorphs	.	78 per cent
		Eosinophiles . .	.	0 ,,
		Basophiles . .	.	1 ,,
		Lymphocytes (small) .	.	10·5 ,,
		Lymphocytes (large) .	.	5 ,,
		Large hyaline cells .	.	3 ,,
		Transitional cells . .	.	2·5 ,,
7th	9,800	Neutrophile polymorphs	.	72 per cent
		Eosinophiles . .	.	0 ,,
		Basophiles . .	.	0 ,,
		Lymphocytes (small) .	.	12 ,,
		Lymphocytes (large) .	.	8 ,,
		Large hyaline cells .	.	2 ,,
		Transitional cells . .	.	3 ,,

On the eighth day the leucocyte count had fallen to 7800, the cerebro-spinal fluid being almost clear. On the following day a recrudescence occurred, meningococci reappearing in the cerebro-spinal fluid and the symptoms of meningitis increasing in intensity ; on the tenth day the leucocyte count showed an increase to 17,800. The patient eventually recovered after a course of 15 days.

A *subacute case* with a total leucocyte count of 17,000 had the following differential count :

Neutrophile polymorphs	.	.	.	86 per cent.	
Eosinophiles	.	.	.	1	,,
Basophiles	.	.	.	1·5	,,
Lymphocytes (small)	.	.	.	3	,,
Lymphocytes (large)	.	.	.	4	,,
Large hyaline cells	.	.	.	3	,,
Transitional cells	.	.	.	1·5	,,

Dow has stated that eosinophiles are always absent in acute fatal cases, but the observations in our series do not support this view. We have found eosinophiles present both in acute fatal cases and in acute cases recovering after a short course, as well as in recrudescent and subacute cases.

The above tables also show the relative diminution of the lymphocytes as the polymorphs increase.

The Leucocytes in Relation to the Type of Case.—On the whole, the leucocyte counts are higher in the acute and more severe cases. The general findings in the various types of case are given below.

Fulminating Type.—Only one fulminating case was investigated ; on the first day of illness the leucocytes were found to be 22,000 per c.mm. The patient died within 36 hours of the onset.

Acute Fatal Type.—Of five acute fatal cases dying within 3-7 days of the onset of illness, no case at any time during the course exhibited a cell count of under 16,200 ; all cases at some time showed over 20,000 leucocytes per c.mm. and two had over 30,000.

Progressively Purulent Type.—Three cases dying in 7-10 days were examined ; all had over 20,000 leucocytes at some time during the course, while two showed 30,000 white cells per c.mm.

Acute Cases recovering after a Short Course.—Of seven cases examined, six had over 20,000 leucocytes per c.mm. at some time during the course, and four patients had over 30,000 per c.mm. on first coming under observation—not later than the third or fourth day of the disease. Another showed 23,000 on the second day, and the remaining two had 16,000 and 14,600 respectively when first examined on the fourth day of illness. The leucocyte count in the last case increased to 16,200 on the 5th day. In all seven cases the number of leucocytes steadily diminished towards the termination of the course. In one, however, who was most severely ill during a course of 14 days, the leucocyte count, from 16,000 on

the first day of observation (fourth day of disease), increased to 31,800 on the 13th day—the day preceding that of recovery.

Acute Cases becoming Subacute.—One case only was examined ; a leucocytosis was present varying from 28,000 to 12,000 cells per c.mm. throughout a course of 23 days.   As a rule the leucocyte count was between 20,000 and 12,000, on only two occasions being over 20,000.   The patient recovered.

Recrudescent Cases (11-44 days).—Five cases examined.   In all, the leucocytosis generally was moderate—10,000-20,000.   On one occasion only, in each of two cases, did the leucocytes reach above 20,000 per c.mm.—in one case this occurred on the day following his admission to hospital (3rd day of disease), and in the second case at the beginning of a recrudescence on the 16th day of the disease.   Throughout the course the leucocytes tended to diminish with improvement in the condition of the patient, but exhibited a distinct increase with the recrudescences.

Subacute Cases.—Nine cases were examined.   There was a general tendency for the leucocyte counts to be moderate—10,000-20,000 ;   when first coming under observation the count was frequently higher, the highest being 25,000.   Six cases had counts of over 20,000, and three of 10,600 to 11,200.   During the course the leucocytes steadily diminished in number.

The Leucocytes in Relation to Purpuric Eruptions.—The leucocytes were counted in ten cases exhibiting purpuric rashes.   All had over 20,000 leucocytes in the earlier part of their courses. Four cases, two of whom gave positive blood cultures, exhibited between 33,600 and 38,600 leucocytes per c.mm. when first they came under observation.   Three had between 20,600 and 26,800 when first seen, and three others, 17,200 to 19,600.   The latter three patients each showed over 20,000 leucocytes when counted two days later.

Of 21 cases without purpuric rashes, three had over 35,000 leucocytes when first counted, eight between 20,000 and 30,000, and ten between 10,000 and 20,000.

It is thus evident that high leucocyte counts may be met with whether a purpuric rash be present or not, but that the lower counts are usually confined to cases without such an eruption.

The Leucocytes in Relation to Pyrexia.—Apart from the return to normal of both the number of leucocytes and the temperature at the termination of the course of the disease, the leucocyte count bears no relation to the degree of pyrexia on any particular day.

The highest count was 45,000 in a patient acutely ill on the third day of disease whose temperature was 104° F. A second case, severely ill, with a temperature of 103·3° F., on the fifth day of illness, had only 25,400 leucocytes. A third case, acutely ill on the fifth day of illness, had a temperature of 99° F. and 9000 leucocytes. A fourth patient, on the day preceding the end of an acute course of fourteen days, exhibited a temperature of 98·4°-99° F. with 31,000 leucocytes. A fifth case, running an acute short course of eight days, had on the second day a normal temperature and 23,000 leucocytes; two days later his general condition improved, but the temperature varied from normal to 100·6° F. and the leucocytes had fallen to 8200; on the following day, although the temperature showed the same variations, the leucocytes were only 7800.

As regards the relation to the general temperature curve in the fulminating, acute fatal, and progressively purulent types, the leucocyte counts tend to remain high, usually over 15,000 throughout the course, although the temperature curve may show marked remissions.

In acute cases recovering after a short course the leucocytosis as a rule tends to persist throughout the course irrespective of the temperature curve, even though it may be normal during part of the illness. In almost every case the temperature reached and remained normal before the leucocytes approached their normal figure.

In recrudescent cases the leucocyte count usually falls between the recrudescences. The leucocytes may or may not reach their normal number before the temperature falls at the termination of the course.

In about half the subacute cases the leucocytes reach normal at the same time or shortly after the temperature curve, but in the remainder they do not fall to normal until a considerable time after the temperature.

Relation of Leucocytes in the Blood to the Characters of the Cerebro-spinal Fluid.—(1) *Appearance of the Fluid.*—As a general rule, the greater the density of the cerebro-spinal fluid the greater is the degree of leucocytosis in the blood.

(a) *Purulent Fluids* (yellowish—with a well-marked deposit of pus).—Nineteen leucocyte counts were made at times when lumbar puncture revealed purulent fluids; the results are shown below :

Leucocyte Counts.	Number of times found.	Number per cent.
Under 10,000	0	0
10,000–15,000	1	5·26 %
15,000–20,000	5	26·31 %
Over 20,000	13	68·42 %

(b) *Turbid Fluids* (*i.e.* whitish fluids of less density than those mentioned above).—Forty-seven leucocyte counts were done in association with the withdrawal of turbid fluids on lumbar puncture.

The following table shows the results obtained :

Leucocyte Counts.	Number of times found.	Number per cent.
Under 10,000	0	0
10,000–15,000	17	37·17 %
15,000–20,000	12	25·53 %
Over 20,000	18	38·3 %

(2) *Presence or Absence of Meningococci.*—Of 108 leucocyte counts 58 were performed at times when meningococci were present in the cerebro-spinal fluid, and 50 on occasions when these organisms were absent. The results are shown in the following table :

Meningococci present.			Meningococci absent.		
Leucocyte Counts.	Number of times found.	Per cent.	Leucocyte Counts.	Number of times found.	Per cent.
Under 10,000	2	3·448 %	Under 10,000	10	20 %
10,000–15,000	16	27·586 %	10,000–15,000	20	40 %
15,000–20,000	14	24·137 %	15,000–20,000	11	22 %
Over 20,000	26	44·827 %	Over 20,000	9	18 %

A study of the above table shows that of 58 examinations made when meningococci were present in the cerebro-spinal fluid, in 31 per cent there were less than 15,000 leucocytes per c.mm. in the blood, and in 69 per cent over 15,000 per c.mm. Of 50 examinations made when meningococci were absent from the cerebro-spinal fluid 60 per cent showed under 15,000 leucocytes per c.mm. in the blood and 40 per cent over 15,000.

It is thus apparent that in the majority of cases the greater leucocytosis is associated with the presence of meningococci in the

cerebro-spinal fluid and the lower leucocyte counts with absence of organisms.

Relation of Leucocytes to Serum Disease.—Fourteen of the above cases treated with anti-meningococcal serum developed serum reactions, together with a rash, during the course; in eight of these the leucocytes had been estimated both before and at the time of the appearance of the sero-toxic rash with sufficient exactitude as to demonstrate the fact that such rashes have practically no effect upon the leucocyte count. Von Pirquet and Schinck found a leucopenia due to the diminution of polymorphonuclear cells, but this observation we were unable to confirm.

Leucocytosis in Relation to Prognosis.—In both fatal and nonfatal cases the leucocyte counts may be high when the patient first comes under observation; in non-fatal cases, however, the number of leucocytes shows a general tendency to become lower as the case progresses. On the other hand, in fatal cases the leucocytes as a rule do not exhibit this tendency to diminish, but the count remains fairly high, seldom falling below 15,000 per c.mm. at any time during the course. A rise in the leucocyte count during the course of the disease is usually indicative of a recrudescence of meningitis, whereas a decrease in the degree of leucocytes is of favourable significance.

MENINGOCOCCI IN THE BLOOD

Since Gwyn, in 1899, first reported the cultivation of the meningococcus from the blood of a case of cerebro-spinal fever, a number of observers have succeeded in obtaining similar blood-cultures. The proportion of cases, however, in which the organisms can be isolated from the blood is relatively small; Elser and Huntoon, for instance, in 1909 reported that the meningococcus was obtained by means of blood-culture in 11 of a series of 42 cases.

It has already been pointed out, in the section dealing with the mode of invasion by the meningococcus (Chapter V.), that in all probability the organism is carried from the naso-pharynx to the meninges by the blood stream. Consequently, if cultivations from the blood be taken during the pre-meningitic stage of the disease a positive result should be obtained. Unfortunately, however, it is very seldom that patients come under observation at such an early stage of the disease, and when this does happen cerebro-spinal fever is rarely diagnosed until the appearance of

meningitic symptoms. One case, however, in which we were able to isolate meningococci from the blood stream prior to the appearance of meningitis, that is, while the cerebro-spinal fluid was still clear and free from both meningococci and an increased cell content, is fully described on p. 63 (Case II.). As a general rule, as stated previously, the meningococcus leaves the blood stream and localises in the subarachnoid space ; consequently, in the majority of cases blood cultures would not be expected to yield positive results when meningitic symptoms have become well marked. In some cases, however, the blood infection appears to be of such overwhelming intensity that the patient dies in a relatively short time, furnishing an example of a fulminating type of the disease. In such cases the meningitis may be comparatively slight, and although meningococci are found present in the cerebro-spinal fluid, not infrequently the organisms persist in the blood stream even in the presence of meningitis, yielding positive blood cultures. A haemorrhagic rash is almost always present, and occasionally meningococci may be seen in blood films taken from the ear or from a purpuric patch. Case XIV. is an example of this type of case. Positive blood cultures have been obtained in similar cases by Cochez and Lemaire, Jacobitz, Martini and Rohde, Lenhartz, Robinson, Dieudonné, Duval, Shircore and Ross, Solly, Drury, A. C. Coles and Denehy.

In a few cases the organisms, instead of settling in the meninges, persist in the blood stream, giving rise to a true meningococcal septicaemia, in which meningitis never appears ; occasionally, structures other than the meninges may be attacked, e.g. the valves of the heart. In such cases blood cultures are positive. Case LIX. (p. 347) is an example ; others have been described by Andrewes, Pybus and Herringham, and are mentioned in Chapter XIV. (p. 345).

Occasionally a secondary blood infection may develop owing, apparently, to meningococci, having previously left the blood stream to become localised in the meninges, being reabsorbed therefrom into the circulation. A similar condition results in monkeys at the height of the meningitis produced by the intrathecal inoculation of meningococci. This view accounts for the fact that blood cultures have occasionally been positive comparatively late in the disease.

Method of Blood Culture.—The skin having been sterilised, 10 c.c. of blood are drawn off from the median basilic vein with a sterile glass syringe in the usual way ; the blood is then inoculated straight into a large tube or flask containing about 50 c.c. of ordinary

bouillon. The tube is placed in the incubator at 37° C. Growth occurs in from 24 to 48 hours.

ANTIBODIES IN THE BLOOD

Agglutinins.—Von Lingelsheim in 1906 reported that reliable agglutination results could be obtained by using the serum of patients suffering from cerebro-spinal fever against killed meningococcus culture. In testing 593 samples of serum, this observer noted positive results in 218 cases; agglutination occurring in a dilution 1 : 25 was regarded as positive. M'Gregor, in examining the blood of 75 cases of cerebro-spinal fever (400 observations in all), arrived at the following conclusions : In acutely fatal cases there is an entire absence of agglutinins ; the degree of agglutinating power of the serum developing in any particular patient depends upon the initial features of the case, being proportional to the acuteness of onset, the degree of primary toxaemia, and the amount of reaction manifested ; agglutinins are produced only in response to the early toxaemic phenomena and appear to be independent of the subsequent course of the case. Elser and Huntoon, however, rightly maintained that the agglutination results obtained with a given serum largely depend upon the strain of meningococcus used in the test. They mention two sera from cases of cerebro-spinal fever which agglutinated one strain of meningococci in a dilution of 1 : 4000, but with four other strains agglutination did not occur in any higher dilution than 1 : 50.

Foster and Gaskell, in a few chronic cases whose serum was tested against their own strains of meningococcus, found that while agglutination may take place with a dilution as high as 1 : 1000, in other cases the agglutinating power is even below that of normal serum.

To determine the extent of the formation of specific agglutinins in the blood, we carried out observations on 52 cases of cerebrospinal fever, either during the course, in convalescence, or after recovery from the disease. Whenever possible, during the illness, the meningococci isolated from the patient's cerebro-spinal fluid were used for testing against the blood serum ; in other cases the organism obtained from the naso-pharynx or stock killed cultures were employed. In the earlier investigations emulsions of Gordon's Types I., II., and III. cocci were each tested against the patient's serum, but later Type IV. was added. The macroscopic method,

similar to that described in Chapter II. (p. 18) with the exception that the serum to be tested is substituted for the type serum, with incubation at 55° C. was employed throughout ; 24 hours were allowed for the reaction to be completed.

The following table shows the results obtained, in relation to the day of illness, during the course of the disease (13 cases) :

TABLE XX

FORMATION OF AGGLUTININS DURING THE COURSE OF CEREBRO-SPINAL FEVER

(+ + = complete agglutination ; + = partial agglutination ; − + = trace of agglutination ; − = no agglutination (negative))

Day of Disease.	Meningococci used.	Result.	Remarks.
2nd	Patient's (Type I.)	− 1 : 10 downwards	Recovered 10th day of illness.
3rd	Types I., II., and III.	− 1 : 10 downwards	An abortive case (Type II.).
3rd	Patient's (Type I.)	− + 1 : 30, − 1 : 40	− 1 : 10 downwards 22 days later.
3rd	Patient's (Type III.)	+ + 1 : 20, 1 : 40, and 1 : 80 + 1 : 160 − 1 : 320 down.	Recovered 14th day of illness.
4th	Patient's (Type I.)	+ + 1 : 10, − + 1 : 20 − 1 : 40 downwards	Fatal: Progressively purulent type.
5th	Patient's (Type II.)	+ 1 : 20, − 1 : 30 down.	Recovered in two weeks.
5th	Patient's (Type III.)	− 1 : 20 downwards	Recovered 14th day of illness.
7th	Patient's (Type III.)	− + 1 : 8, − 1 : 16 down.	Fatal on 31st day of illness.
7th	Patient's (Type I.)	− 1 : 10 downwards	Recovered 10th day of illness.
11th	Types I., II., III., and IV.	− 1 : 10 downwards	Recovered 14th day of illness.
12th	Type I. (Stock)	− 1 : 20 downwards	A Type I. case.
13th	Types I., II., III., and IV.	− + 1 : 20 to 1 : 60 Type I., − 1 : 80 down. Type I. ; − 1 : 20 down. Types II., III., and IV.	A Type I. case ; recovered 14th day of illness.
13th	Types I., II., and III.	− 1 : 10 down. All 3 Types	A Type I. case.

The following table shows the results obtained in patients recovered from the disease (39 cases).

TABLE XXI

Agglutinins in Recovered Cases of Cerebro-spinal Fever

(+ + = complete agglutination ; + = partial agglutination ;
 − + = trace of agglutination ; − = no agglutination)

Time after Recovery.	Types of Meningococci used.	Result.	Remarks.
4 days	I., II., III., & IV.	− 1 : 20 downwards	...
5 ,,	I.	− 1 : 20 ,,	Type I. case.
12 ,,	I.	− 1 : 20 ,,	,, I. ,,
2 weeks	I.	− 1 : 20 ,,	,, I. ,,
3 ,,	III.	− 1 : 20 ,,	,, III. ,,
3 ,,	I., II., III., & IV.	− 1 : 20 ,,	,, III. ,,
4 ,,	I., II., III., & IV.	− 1 : 20 ,,	...
4 ,,	I., II., & III.	− 1 : 10 ,,	...
4 ,,	I., II., & III.	− 1 : 10 ,,	...
4 ,,	II.	− 1 : 20 ,,	Type II. case.
5 ,,	I., II., & III.	− 1 : 20 ,,	...
5 ,,	I., II., & III.	− 1 : 20 ,,	...
6 ,,	I., II., & III.	+ + 1 : 10 to 1 : 40, + 1 : 80, − 1 : 160 downwards to Type II., − 1 : 10 downwards to Types I. & III.	...
6 ,,	I., II., III., & IV.	− 1 : 20 downwards	...
6 ,,	I., II., III., & IV.	− 1 : 20 ,,	...
6 ,,	Patient's—from naso-pharynx (Type II.)	− 1 : 10 ,,	Type II. case.
6 ,,	II.	− 1 : 10 ,,	,, II. ,,
6 ,,	III.	− 1 : 10 ,,	,, III. ,,
6 ,,	I., II., III., & IV.	− 1 : 10 ,,	...
7 ,,	I., II., III., & IV.	− 1 : 20 ,,	...
8 ,,	I., II., & III.	− 1 : 10 ,,	...
8 ,,	I., II., III., & IV.	− 1 : 10 ,,	...
8 ,,	I., II., III., & IV.	− 1 : 10 ,,	...
8 ,,	I., II., III., & IV.	− 1 : 10 ,,	...
8 ,,	II.	− 1 : 10 ,,	Type II. case.
10 ,,	I., II., & III.	+ 1 : 40 and 1 : 80 Type II. − 1 : 160 Type II. − 1 : 40 downwards, Types I. & III.	Two weeks later all agglutinins had disappeared.
3 months	I., II., III., & IV.	− 1 : 10 downwards	...
3 ,,	I., II., III., & IV.	− 1 : 10 ,,	...
3 ,,	I., II., III., & IV.	− 1 : 10 ,,	...
3 ,,	I., II., III., & IV.	− 1 : 10 ,,	...
3 ,,	I., II., III., & IV.	− 1 : 10 ,,	...
3 ,,	I., II., III., & IV.	− 1 : 10 ,,	...
4 ,,	I., II., III., & IV.	− 1 : 10 ,,	...
6 ,,	I., II., III., & IV.	− 1 : 5 ,,	...
6 ,,	I., II., III., & IV.	− 1 : 10 ,,	...
7 ,,	I., II., & III.	+ 1 : 10, − + 1 : 20, 1 : 40, and 1 : 80 Type II.; − 1 : 10 downwards Types I., III., and IV.	...
7 ,,	I., II., III., & IV.	− 1 : 20 downwards	...
8 ,,	I., II., III., & IV.	− 1 : 20 ,,	...
10 ,,	I., II., III., & IV.	− 1 : 20 ,,	...

From the above tables it will be seen that :

(1) The formation of agglutinin is very irregular.

(2) The presence of agglutinin bears no relation to prognosis.

(3) Agglutinin if present tends to disappear during the course of illness and, as a rule, cannot be detected when the patient has recovered.

Of 39 recovered cases, agglutinins were detected in three cases only, and then in no higher dilution than 1 : 80. We were not able to satisfy ourselves that their presence bore any relation to the acuteness of onset or the type of case.

During the Belfast epidemic (1907–8) Symmers and Wilson found that the blood serum of patients suffering from cerebro-spinal fever had a distinct agglutinating action on bacilli of the alcaligenes group. In explanation of this Wilson considered it probable that infection with certain micro-organisms (*e.g.* meningo-coccus) led to an alteration in the bacterial flora of the intestine ; as a result of this secondary auto-infection, agglutinins are formed for the intestinal organisms as well as for the primary infecting agent. Elser and Huntoon tend to confirm the observations of Symmers and Wilson and to offer a similar explanation. They found that in rabbits injections of meningococci rendered the mucosa of the intestinal tract more permeable to typhoid bacilli administered with food. Rabbits thus treated developed agglutinins for the organism administered by the mouth, while no agglutinins were detected in the serum of controls which were fed with typhoid bacilli but received no meningococcus injection.

Opsonins.—M'Gregor from a study of the opsonic indices in a series of 55 cases of cerebro-spinal fever (175 observations) concluded that the highest index occurs chiefly in those cases exhibiting acute initial symptoms of short duration, and that it tends to reach its maximum during the second and third weeks of the disease. He also considered that a high opsonic index was a sign of prompt reaction to a severe infection ; nevertheless, the test was of no value in determining prognosis as cases with a low index often recover while those exhibiting a high index may die.

Houston and Rankin, as the result of a series of 370 observations, found that a high positive opsonic index is present in most cases after the fifth or sixth day of illness. Also, these observers state that while normal serum or the serum of patients suffering from diseases other than cerebro-spinal fever has little effect on

meningococci, the serum of cases of the latter disease has a markedly phagocytic action ; they succeeded in obtaining positive phagocytic reactions in 98 per cent of cases of meningococcal meningitis after the sixth day of disease. In 1909 Davis concluded that phagocytosis of the meningococcus was usually more marked with the serum from cerebro-spinal fever cases than that from normal persons, although the results were inclined to be variable. Sophian, as a result of his investigations, found that opsonic determinations gave readings which were often irregular and unreliable ; further, the results varied widely with different strains of meningococci.

The conclusion is that the opsonic test, owing to its variability, is of little or no value in the diagnosis of cerebro-spinal fever.

Complement-Fixation Bodies.—With the sera of three patients suffering from cerebro-spinal fever, Meakins in 1907 obtained positive complement-fixation in a dilution of 1 : 80 against a meningococcus antigen. Subsequently, Dopter, Cohen, and Schumann also demonstrated, by means of complement-fixation, the presence of immune bodies in the blood of cerebro-spinal fever cases. Sophian in 1913, however, found that if non-specific bacterial antigens be used, there occurred considerable cross-fixation between the meningococcus and the gonococcus and their respective sera. Consequently, since the majority of patients suffering from gonococcus infection show immune bodies by complement-fixation, it would be necessary for the purpose of absolute diagnosis to employ specific bacterial antigens which do not give cross-fixation with other sera. M'Neil, therefore, prepared a specific antigen with which he obtained high and distinct fixation, no cross-fixation occurring with the gonococcus.

The method of preparation of M'Neil's antigen is as follows :

The culture of meningococcus is grown on slants of salt-free veal agar, neutral to phenolphthalein, for 18-24 hours. It is then washed off in distilled water and heated in a water bath for two hours at 56° C. ; following this, the emulsion is centrifuged for about 20 minutes. The resulting supernatant fluid is passed through a medium Berkefeld filter, placed in hermetically sealed capsules, and finally heated to 56° C. for half an hour on two successive days to ensure sterility. Stored in an ice-box the antigen keeps for several months. Before using, one part of 9 per cent saline solution is added to nine parts of antigen, and the mixture titrated.

Bactericidal Substances.—According to Davis, the serum of patients suffering from cerebro-spinal fever acquires definite bacteri-

cidal properties against the meningococcus, more especially late in the disease. He found that meningococci, when placed in contact with the blood from several cases obtained at various times between the tenth day and seventh week of illness, were rapidly and invariably destroyed, the media being sterile usually after three hours. To some extent normal serum exerted the same influence, but the result was much more marked in the case of blood from cerebrospinal fever patients.

Clinically, Mackenzie and Martin claimed favourable results by treating cases of the disease with intrathecal injection of the patient's own serum as well as that obtained from the blood of recovered cases. A few other successful cases have been reported by various observers. In one of our cases the result was not satisfactory (*vide* p. 452).

CHAPTER XII

DIAGNOSIS OF CEREBRO-SPINAL FEVER

EARLY diagnosis in cerebro-spinal fever is of paramount importance as results have invariably shown that the earlier treatment is begun, the greater are the chances of the patient's ultimate recovery from the disease (*vide* Chapter XVIII. p. 403). Conclusive diagnosis cannot be made on clinical evidence alone ; the question is rather what factors justify the opinion that a particular patient is probably suffering from cerebro-spinal fever and demands lumbar puncture to confirm the provisional diagnosis. This aspect is important as in both civil and military practice, the general practitioner or regimental medical officer has usually to arrive at a conclusion on the clinical examination only, as if a suspected case is met with, it usually passes out of his hands to an isolation hospital or ward.

In the early stage of the disease, before the development of definite meningitis, diagnosis is extremely difficult and often impossible. Certain facts, however, may cause one to suspect the presence of cerebro-spinal fever, especially when the disease is prevalent, and so lead to close observation being kept on the patient.

A sudden onset commencing with rigors, gradually increasing headache, and the appearance of vomiting within the first 24 hours is highly suggestive ; such an onset occurred in 50 of 70 consecutive cases of our series. In 22 it was preceded by a short period of malaise (*vide* Onset, Chapter VI.). Vomiting had occurred in 61 of the cases, including even those in whom the onset had been more gradual. Of the nine exceptions, three showed a gradual onset, two were mild, subacute cases, and two were of the fulminating type, dying within 36 hours of the onset.

A few cases may come under observation on the first day of illness, and prior to the invasion of the meninges by the organism, exhibiting a petechial or purpuric rash. The latter eruption occurring with the characteristic sudden and abrupt onset justifies the administration of anti-meningococcal serum even though the cerebro-spinal fluid be clear and reveal no abnormality. One such case (Case II. p. 63) has already been described, the only symptoms being pyrexia and the presence of purpuric spots. The cerebro-spinal fluid was clear, and upon subsequent examination showed no abnormality, cultures remaining sterile. Anti-meningococcal serum was at once given intra-muscularly. By the evening, signs of early meningitis developed, and lumbar puncture revealed a fluid slightly turbid and containing meningococci ; serum was then given intrathecally. Although the rash was characteristic of that seen in fulminating cases, by the sixth day of illness the patient had recovered. It is rare, however, to meet with such a case, and, as a rule, the rash is of little help in early diagnosis for the following reasons :

(1) There may be no rash. (A rash was observed in about 50 per cent of our patients.)

(2) A macular rash frequently does not appear before the third or fourth day.

The presence of the rash, therefore, cannot be relied upon, and is only of assistance in relatively few cases.

The characteristic muscular rigidity does not begin to appear until the meninges are invaded by organisms ; in the presence of such rigidity the cerebro-spinal fluid may still be clear to the naked eye, but diplococci are seen on microscopical examination of the centrifugalised deposit (e.g. Case IV. p. 70). A certain degree of rigidity in the neck muscles is one of the earliest signs and is of cardinal importance ; the cervical muscles, therefore, must be carefully examined in all cases in which cerebro-spinal fever is suspected. Head retraction as a sign is useless if diagnosis is to be made early, as it seldom develops before the third or fourth day of illness, and in many adult cases is absent throughout the course. A valuable method of estimating the degree of neck rigidity is described on p. 108 (Chapter VI.). With the patient lying on his back, the observer places his hand beneath the head and endeavours gently to draw it forward. In the presence of meningitis, with the occasional exception of the tuberculous variety, the head cannot be brought forward more than about two inches beyond

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the line of the long axis of the body ; more often, indeed, it cannot be flexed past this line.   The sign is sometimes present within even 5 or 6 hours of the onset, and frequently within 12 hours ; in fulminating cases it may be absent, but in such cases its presence is not usually necessary to arrive at a diagnosis.   In one case seen early on the first day, within five or six hours of the onset, the head could not be brought more than two to three inches beyond the vertical line of the body, although the cerebro-spinal fluid was perfectly clear and showed neither an increased cell content nor organisms ;   within 18 hours, however, neck rigidity was well marked and the cerebro-spinal fluid turbid.   In another case received within 24 hours of the onset, and whose cerebro-spinal fluid had already become purulent, the head could not be flexed beyond the perpendicular.

Of all cases on admission to hospital, irrespective both of the type of case and of the day of disease, this neck sign was present in over 80 per cent.   Of three cases met with in the pre-meningitic stage it was absent in two ; in all three, however, it was well marked within 12-24 hours of the onset.   Excluding fulminating cases and those admitted comatose, neck rigidity was demonstrated in 93 per cent.   If profound collapse be present during the initial stage of meningitis, cervical rigidity may be absent ; in such cases the temperature is frequently subnormal.

Kernig's sign is one of great diagnostic value in all cases above the age of two years.   Of the three variations of the sign described on p. 112 (Chapter VI.) we have found the following the most useful : With the patient lying supine, the thigh is placed at a right angle with the trunk ; maintaining the thigh in this position, an attempt is made to extend the leg on the thigh.   If it is found impossible to bring the leg beyond an angle of 45° with a horizontal line through the knee and at a right angle to the thigh, the sign is considered positive (Plate V. p. 114).   Kernig's sign is often present within 12 hours of the onset, can usually be obtained within 18 hours, and is almost invariably positive at the end of 24.   For instance, in the case received early on the first day (Case III. p. 69) within 5-6 hours of the onset, the sign was absent, but some slight rigidity of the hamstrings could be demonstrated, being somewhat greater on the right side than on the left.   In a case received within 24 hours of the onset, Kernig's sign was very well marked.   The sign is of no value in infants below the age of two years, owing to a certain amount of physiological muscular rigidity which is

often present at this age ; consequently Kernig's sign may occasionally be obtained in normal infants.

Of all cases on admission to hospital, irrespective of the type of disease and day of illness, we found Kernig's sign present in 85 per cent. In addition to the pre-meningitic stage of the disease, the sign is often absent in coma and in cases of the fulminating type ; it may also be difficult to detect in very old or very young patients. The analysis of Kernig's sign in relation to the day of disease on which the patient first came under observation (Chapter VI. p. 114) further illustrates its value.

Various conditions, in addition to other forms of meningitis, which may give rise to a positive Kernig's sign are : Disuse of the lower limbs as, for instance, remaining in bed in a recumbent position for some days, upper neurone lesions of the spinal cord (owing to spasticity), sciatica, uraemia, cerebral or meningeal haemorrhage, and lesions involving the base of the brain. With the exception of the latter four, however, these conditions are rarely mistaken for meningitis.

As regards Brudzinski's signs (Chapter VI. p. 116), they are of secondary importance only, and in our experience are seldom obtained in the absence of Kernig's sign. Of the two, the identical contralateral reflex is the more constant.

Early delirium occurring in a pyrexial patient, especially if co-existing with headache, is of some significance and should lead to an examination for muscular rigidity. In infants, tension and bulging of the anterior fontanelle is an early and most important sign ; when the fontanelle is closed, as in older children, Macewen's sign (p. 132) may frequently be demonstrated. In adults the thickness of the skull renders this sign uncertain.

A comparatively slow pulse, associated with a high temperature, is often of considerable value in doubtful cases. Of 68 consecutive cases the pulse rate was below 98 in 47, and 84 or under in 39 ; of the latter cases the temperature was 100° F. or over in all, and above 101° F. in 60 per cent. Irregularities of respiration also favour a diagnosis of meningitis.

Retention of urine, when present, is an important symptom, especially in association with other signs ; it sometimes appears within 24 hours of the onset. Retention with overflow may occur and may be mistaken for true paralytic incontinence.

Associated with general hyperaesthesia, one may frequently find that on attempting to elicit the plantar reflex, the patient's

leg is actively withdrawn ; in the presence of delirium or stupor, this sign is often of considerable significance. It was seen in 38 of 60 consecutive cases on admission to hospital. The abdominal reflexes are frequently absent, but the condition of the tendon reflexes is of no diagnostic value.

Herpes may be present in relatively late cases, but as this symptom seldom appears before the fourth day, the case should have been diagnosed earlier. Tache cérébrale is easily demonstrated but is present in too many other conditions to be of any significance in the diagnosis of meningitis.

The following tables summarise the chief diagnostic features of the disease :

A. **Chief and Characteristic Diagnostic Signs.**
1. Sudden onset (in a patient previously well or complaining only of a " cold ") :
   - *a.* Rigors.
   - *b.* Increasingly severe headache.
   - *c.* Vomiting.
2. Cervical muscular rigidity : flexion sign.
3. Kernig's sign.
4. In infants, tension and bulging of anterior fontanelle.

B. **Secondary Signs, of Value when Present** (especially in association with those under A).
1. Petechial or purpuric rash.
2. Bladder condition :
   - *a.* Retention.
   - *b.* Incontinence.
3. Plantar stimulation—active withdrawal of leg.
4. Pulse - temperature ratio = comparatively slow pulse with high temperature.

The diagnosis is finally confirmed by an examination of the cerebro-spinal fluid obtained by lumbar puncture. The fluid withdrawn during the pre-meningitic stage of the disease is quite clear to the naked eye and may reveal no meningococci ; the potassium permanganate test (Chapter X. p. 255), however, may occasionally be positive. At a slightly later stage, when muscular rigidity is just commencing, the fluid may still be clear to the naked eye but Gram-negative diplococci are found on examination of the centrifugalised deposit (*e.g.* Case IV. p. 70). After the elapse of a period varying between 12 and 24 hours of the onset, the cerebro-

spinal fluid becomes turbid or purulent and on microscopical examination shows a vast predominance of polymorphonuclear pus cells ; some mononuclear cells as a rule are also present, but they are almost always in a minority. Gram-negative diplococci, intracellular, extracellular, or both, can usually be made out, although sometimes only after prolonged search ; for all practical purposes these diplococci can be taken as diagnostic. Further and absolute confirmation is, of course, obtained on cultivation of the organism.

In our experience, the precipitin test as applied to the cerebrospinal fluid (Chapter X. p. 272) is too inconstant to be of any definite value in diagnosis, and agglutination reactions with the patient's serum are far too variable to yield any satisfactory results (Chapter XI. p. 298).

A naso-pharyngeal swab should be taken as early as possible in the disease. If difficulty is experienced in finding Gram-negative cocci on direct microscopical examination of the centrifugalised deposit in the cerebro-spinal fluid, or if organisms fail to grow on culture, the result of the naso-pharyngeal swab is often helpful in making a diagnosis of cerebro-spinal fever, in contra-distinction to other forms of meningitis.

DIFFERENTIAL DIAGNOSIS

The various pathological conditions from which it is necessary to distinguish cerebro-spinal fever may be conveniently classified under the following headings :

    I. Acute infective processes.
   II. Diseases of the central nervous system other than meningitis.
 III. Miscellaneous conditions.
 IV. Other forms of meningitis.

In discussing the differential diagnosis of the disease, examples will be mentioned which in our own experience have given rise to erroneous diagnosis. Such cases fall into two groups :

(a) Cases of true cerebro-spinal fever regarded elsewhere, prior to admission, as examples of other diseases, or sent into hospital with a diagnosis other than that of cerebro-spinal fever.

(b) Cases of other diseases sent into hospital as suspected cases of cerebro-spinal fever.

I. Acute Infective Processes

Influenza.—The clinical differentiation of cerebro-spinal fever from influenza often presents considerable difficulty, particularly as the diagnosis of the latter is arrived at chiefly by a process of excluding other conditions. Both influenza and cerebro-spinal fever in its early stages show many features in common—a sudden onset, headache, pyrexia, and pain and stiffness in the muscles. On the first day accurate diagnosis may be impossible ; points of difference, however, are as follows : Vomiting is much more frequent in cerebro-spinal fever, although it may be present in the gastric type of influenza. A relatively slow pulse in proportion to the temperature towards the end of the first day favours cerebro-spinal fever ; by this time Kernig's sign may also be detected. By the second day, the case of influenza is usually a little better, but not so the cerebro-spinal fever patient. In the latter, cervical rigidity is then more pronounced and flexion of the head may be impossible ; Kernig's sign also should be positive. With influenza there may be some rigidity of the hamstring muscles, but this seldom amounts to a definite Kernig's sign, nor does it increase as rapidly as in meningitis. In cerebro-spinal fever, active withdrawal of the leg on plantar stimulation may also be demonstrated, while retention of urine is a symptom to be borne in mind. Ciliary hyperaemia is often present in cerebro-spinal fever but absent in influenza.

If there remains any doubt after attention to the above points, lumbar puncture is indicated rather than the opportunity of commencing treatment early be missed. Even then the diagnosis may not be decided, as cases of cerebro-spinal fever show a clear cerebro-spinal fluid during the pre-meningitic stage ; the permanganate test (*vide* p. 255), however, may be suggestive, or microscopical examination of the deposit obtained by centrifugalising the apparently clear fluid may reveal a few Gram-negative diplococci.

Several cases of cerebro-spinal fever have been received by us with a diagnosis of influenza. Of these, three cases were admitted on the first day of illness ; the true nature of the disease was at once suspected in one owing to the presence of a certain amount of cervical rigidity, the " neck sign " being just positive, and also by the fact that the patient had recently vomited ; the cerebro-spinal fluid, however, was quite clear to the naked eye and showed no definite abnormality beyond a positive permanganate (zonal)

reaction (*vide* p. 253). The patient was kept under observation, and early next morning, the signs of meningitis having further developed, a purulent fluid was obtained on lumbar puncture.

Other cases of cerebro-spinal fever regarded as suffering from influenza prior to admission, had exhibited a more gradual onset. The early symptoms had consisted of increasingly severe headache and pain and stiffness in the limbs ; in the majority vomiting had occurred. All were subacute cases, and the true nature of the disease not suspected until increasing drowsiness or delirium appeared towards the third or fourth day, upon which the patient was transferred for investigation. In most of these cases the characteristic signs of meningitis were well marked and they presented no difficulties in diagnosis.

Three subacute cases, which had all been regarded at local hospitals as suffering from severe influenza, were not received by us until the 13th day in two cases and the 14th day in one. Occasional and particularly nocturnal delirium was present in all, and on admission the characteristic signs were easily demonstrated. The onset in each case had been gradual, but vomiting had invariably occurred during the earlier stages of the course.

Another patient was admitted as a case of " influenza with muscular rheumatism " and was sent as such into a general ward early on the second day. The onset had occurred gradually following a period of indisposition (cough and " sore throat " for six days), and consisted of rigors, headache and vomiting. He was received by us next morning still delirious, but with cervical rigidity and Kernig's sign well marked.

Many cases of influenza were admitted as suspected examples of cerebro-spinal fever, while many others were seen from time to time as doubtful cases. Those complicated by some degree of " muscular rheumatism," lumbago, or hysterical symptoms were usually the most difficult to diagnose with any degree of certainty. In no case of influenza, however, even with intense muscular pain or lumbago, was a really definite Kernig's sign ever obtained ; there was frequently some rigidity of the hamstring muscles, varying in degree in different cases. Rigidity of the neck muscles, also, was never really pronounced, apart from the cases showing hysterical symptoms. In no example of influenza was it such as to prevent the head being brought forward well beyond the line of the long axis of the body, in the elicitation of the neck sign previously described. The chin, in most cases,

could be brought almost to the chest, but in others the range was rather more limited. Further, the pulse was usually increased in direct proportion to the temperature, and only in a few cases did vomiting occur with the onset. Two cases of influenza may be mentioned in which it was considered necessary to proceed with lumbar puncture. One was a patient, aged 24, who had suddenly felt ill on the preceding day, complaining of headache, pain in the limbs, and a few hours later, vomiting. On admission to hospital, there was some slight stiffness of the neck; the head could be brought forward about two inches beyond the perpendicular; there was some slight rigidity of the hamstring muscles but no positive Kernig's sign. The patient's mental condition was normal, the temperature 101° F., and the pulse rate 100 per minute. The cerebro-spinal fluid was found to be clear and showed nothing abnormal. The patient rapidly improved. The second case was very similar but vomiting had not occurred; severe lumbago was present, giving rise to a modified Kernig's sign.

Naso-pharyngeal swabs taken from several cases of influenza have invariably given negative results as regards the presence of meningococci.

Pneumonia.—In the early stages this disease closely resembles, and may be mistaken for, cerebro-spinal fever, more particularly if vomiting has occurred and if it is too early for physical signs in the lungs to have developed. In pneumonia, however, neck rigidity is absent or extremely slight and Kernig's sign is not present; the pulse rate is raised in proportion to the temperature, this ratio being continuous. A blood culture taken early in cases of suspected pneumonia, without physical signs, will frequently reveal pneumococci. Should pulmonary signs fail to develop within a day or two and the diagnosis still remain in doubt, lumbar puncture should be performed.

The broncho-pneumonia occasionally complicating cerebro-spinal fever in children may sometimes be so intense as to overshadow the symptoms and signs of meningitis. Also, if both meningitis and pneumonia are recognised, care should be taken not to mistake the condition for meningitis secondary to pneumonia. In our experience, very few adult cases of cerebro-spinal fever had previously been regarded as suffering from pneumonia.

Of adult and adolescent patients suffering from pneumonia and received as cases of suspected cerebro-spinal fever, the majority showed no definite signs of the latter disease. The patients were

flushed, with a high temperature and a proportionately rapid pulse, Kernig's sign and neck rigidity being both absent. Careful examination of the chest often revealed the true condition. In a few cases, however, there was considerably more justification for the suspicion of cerebro-spinal fever. As an example, the following case may be cited :

CASE XLVII. **Pneumonia simulating Cerebro-spinal Fever.** — The patient was admitted with the history that he had felt unwell for three days, complaining of occasional and severe frontal headache, pain in the epigastrium and limbs, and also at the back of neck ; further, he had vomited several times, the last occasion being on the morning of admission, when he felt very much worse. On examination, some degree of photophobia was present, together with considerable drowsiness ; his mental condition was otherwise normal. The head could be flexed well forwards, the chin not quite reaching the chest ; such movement, however, gave rise to a certain amount of pain. Kernig's sign was absent, there being the merest suggestion of increased tonicity in the hamstring muscles. The reflexes showed nothing abnormal, but there was a well-marked tache cérébrale. The heart and lungs both appeared normal, the temperature was 102·8° F., the pulse 120, and the respirations only 24. He was kept under observation and provisionally diagnosed as early pneumonia, the evidence of meningitis not being considered sufficiently strong to demand lumbar puncture. Blood was withdrawn for culture and a naso-pharyngeal swab also taken. Next day he was practically in the same condition, excepting for a complaint of pain on the right side of the chest ; there were no physical signs in the lungs. On the following day, however, impaired resonance was found at the extreme base of the right lung, with a definite patch of bronchial breathing ; the temperature was 103° F., the pulse 124, and the respirations 26. The blood taken on the first day of admission gave a growth of pneumococci, and the naso-pharyngeal swab was negative as regards meningococci.

In infants, pneumonia often gives rise to a condition simulating meningitis (meningism, *vide* p. 317), not infrequently before any signs can be detected in the lungs. In such cases lumbar puncture alone can decide the diagnosis.

Typhoid Fever.—Although at first not easy to diagnose as such, typhoid fever during the early stages should seldom be mistaken for cerebro-spinal fever. Difficulty is likely to arise, not so much with regard to actual cases of cerebro-spinal fever, but rather in considering true typhoid patients as possible cases of the former disease. The two conditions usually resemble each other, during the first week, in a few particulars only—the drowsy, sometimes

delirious, mental state, headache, the relatively slow pulse as compared with the temperature, and possibly in the occurrence of vomiting. A well-recognised difference is that in meningitis headache and delirium co-exist while in typhoid fever they alternate. Further, a leucocyte count is often of assistance, as in cerebrospinal fever a leucocytosis is the rule, but in typhoid a leucopenia is usual. The absence of neck rigidity and Kernig's sign after the second or third day would be conclusive in excluding meningitis.

One patient, seen on the third day of illness, had previously been regarded in an auxiliary hospital as a possible case of typhoid fever, chiefly owing to his extreme drowsiness. When visited, he was delirious and incoherent, with well marked cervical rigidity and a bilateral Kernig's sign. One case of typhoid only was ever received as a possible case of cerebro-spinal fever.

Typhus Fever.—This disease, now rare apart from localised epidemics, is sometimes likely to be mistaken for cerebro-spinal fever ; before the introduction of lumbar puncture, the two conditions were without doubt often confused. The onset in both is similar, consisting of rigors, headache and vomiting ; the latter symptom, however, is much more common in cerebro-spinal fever than in typhus. Delirium and retention of urine also occur in typhus fever but are usually much later in appearing than in meningitis. According to Jeanneret-Minkine, the typhus patient becomes seriously ill only by the fourth day. Further, the purpuric rash of cerebro-spinal fever, if present at all, appears on the first or second day, while in typhus it does not develop before the fourth or fifth day. Typhus eruptions are as a rule maculo-roseolar, and in the opinion of Jeanneret-Minkine, petechial rashes are only seen in about 10 per cent of cases.

It is evident, therefore, that differential symptoms appear more rapidly in cerebro-spinal fever, and by the second day, or at the latest the third, meningitis, if present, should be revealed by the characteristic signs.

One case was admitted elsewhere in the hospital, in which, according to the opinion of a competent authority, the probable diagnosis was typhus fever. The question of cerebro-spinal fever had been raised, but beyond the symptom of extreme drowsiness he bore no resemblance to a case of this disease ; a blotchy erythematous rash with occasional petechia was stated to appear about the 4th or 5th day. The case terminated fatally on the 9th day of illness,

and, on post-mortem examination, pneumonia of the right upper lobe was found.

Septicaemia and Pyaemia.—The pyrexia, rigors and various cutaneous eruptions—erythematous, petechial or purpuric—occurring in these diseases, might well lead to their being mistaken for cerebro-spinal fever. An arthropathy also may occur in either condition. In septicaemia, however, the onset is more insidious, endocarditis is more frequent, and careful examination may reveal a primary focus of infection. Further, splenic enlargement and the absence of neck rigidity and Kernig's sign after the first 24 hours would serve to exclude cerebro-spinal fever.

Measles.—Acute forms of this disease occurring in children may closely simulate cerebro-spinal fever, and during an epidemic of the latter condition lead to difficulties of diagnosis. According to Horder, the specific toxin of measles is capable of exercising an action on the central nervous system, which results in the production of meningeal symptoms.

From time to time, we have seen several cases of measles as suspected cases of cerebro-spinal fever, but the vast majority have borne little or no resemblance to the latter disease. The somewhat common occurrence of cerebro-spinal fever developing during convalescence from measles has already been referred to.

Malignant Smallpox.—According to Milligan, this condition may closely simulate cerebro-spinal fever, chiefly on account of the sudden onset, headache, vomiting, and pain in back. The usual muscular rigidities of meningitis, however, are absent, and on the third or fourth day the characteristic eruption appears.

Acute Rheumatism.—Owing to the pain in the limbs and muscular rigidity, subacute cerebro-spinal fever is occasionally mistaken for acute rheumatism. If an early arthropathy be present the resemblance is further enhanced. Horder mentions two cases of cerebro-spinal fever, occurring in young adults, in which a diagnosis of acute rheumatism had been made on account of the strong clinical resemblance to the latter disease. In one of the patients, in addition to synovitis, profuse sweats with an acid odour were present.

In our own experience, cerebro-spinal fever patients have seldom been regarded as suffering from acute rheumatism, but we found a few subacute cases labelled " muscular rheumatism " (*vide* p. 326).

Acute Follicular Tonsillitis.—This condition may at first give

rise to a suspicion of cerebro-spinal fever, particularly, as we have shown elsewhere (Chapter VI. p. 72), when it is remembered that a " sore throat " sometimes precedes the development of meningitis. The onset of tonsillitis may occur with headache, rigors, and frequently vomiting ; further, the soreness in the throat or tenderness and swelling of the cervical glands may give rise to apparent rigidity of the neck, the patient being reluctant to permit flexion of the head owing to the pain produced in the throat. Kernig's sign, however, is absent, consciousness usually normal, and although congestion of the fauces may be seen in cerebro-spinal fever, it is unusual to find any definite enlargement of the submaxillary or cervical glands as in tonsillitis. Also, in the latter condition the pulse rate is usually raised in proportion to the temperature.

Three cases of acute tonsillitis received into hospital as probable cases of cerebro-spinal fever may be mentioned. Vomiting had occurred in one only ; in all three cases, consciousness was perfectly clear and Kernig's sign was definitely absent in two, the third showing some slight rigidity of the hamstrings. Follicular tonsillitis was seen in each case, two having very large and chronically hypertrophied tonsils ; one of the latter also had considerable oedema of the fauces and uvula. Some limitation in flexion of the head was present in all, for the reasons mentioned above, but without any real rigidity of the posterior cervical muscles. Swollen and tender submaxillary glands were also found in each case, the temperature being raised and the pulse rate proportionally rapid. Naso-pharyngeal swabs, taken in all cases, showed absence of meningococci.

A true meningitis, due to the causative organism in each case, may occur in pneumonia, typhoid fever and, more rarely, influenza. It has also been described as a complication of measles, mumps and typhus fever, while Siemerlung describes a case of meningitis supervening on a definite follicular tonsillitis ; no organisms were found in the cerebro-spinal fluid. In such cases it is not possible definitely to exclude cerebro-spinal fever, since it is well known that in some cases of the latter disease meningococci may escape detection in the films of the cerebro-spinal fluid examined.

In cases of pneumonia and typhoid fever, the pneumococcus and the Bacillus typhosus respectively may occasionally be isolated from the cerebro-spinal fluid in the absence of true meningitis.

In acute infections, the toxic process not infrequently gives rise to a state suggesting meningitis and to which Dupré originally applied the term " meningism." In the so-called cerebro-spinal form of typhoid, for instance, intense nervous symptoms—photophobia, head retraction, muscular rigidity and even convulsions—may develop, occasionally at a relatively early stage of the disease. The cerebro-spinal fluid, however, reveals no abnormality and, on post-mortem examination, no meningitis is apparent.

The question as to whether meningism is entirely due to toxaemia or whether it is dependent upon definite though slight changes in the pia-arachnoid without visible exudate, is not yet satisfactorily determined. According to Oseki, cases of meningism occurring in association with infectious diseases, in most instances have been found to be free from any anatomical change in the meninges. This observer found that in some cases with clinical signs of meningitis, post‑mortem examination revealed no gross microscopical changes beyond the occasional presence of oedema or of slight opacity of the membranes. On microscopical examination, however, acute inflammatory changes were often found, being most marked about the smaller blood vessels, and associated with leucocytic infiltration in the meninges and brain substance.

As regards the cerebro-spinal fluid in cases of meningism, a relative increase in both the amount of fluid obtainable by lumbar puncture and the intrathecal pressure is usual. According to some authors, there may also be a slight increase in the protein content and a moderate lymphocytosis ; the latter conditions, however, we have failed to find in cases of meningism associated with influenza, early pneumonia and gastro-enteritis.

If meningism is at all pronounced, especially in children, it is advisable to perform lumbar puncture in order to exclude meningitis.

In suspected cases of meningitis, on lumbar puncture, an initial difficulty may sometimes be met with—that is, if a few drops of blood escape into the cerebro-spinal fluid during the passage of the needle, the fluid obtained may appear slightly turbid and so give rise to doubt. Centrifugalisation and microscopical examination will, however, reveal the true cause of the apparent turbidity.

II. Conditions of the Central Nervous System other than Meningitis

Cerebral Abscess.—This condition may frequently simulate meningitis, and particularly when the abscess is localised to the

cerebellum.   Cerebral abscesses may be either single or multiple, the former usually being secondary to otitis media.   Features that the condition has in common with cerebro-spinal fever are persistent headache, drowsiness and lethargy, and a relatively slow pulse rate ; vomiting may also be present.   The onset, however, is not usually sudden or abrupt as in meningitis, and although the temperature may be raised in the early stage, as a rule it rapidly becomes subnormal ; optic neuritis is more frequent in cerebral abscess.   In doubtful cases the presence of an ear discharge favours the latter condition, although by no means invariably.   Several patients in our series had old-standing otorrhoea ; meningitis was, however, the obvious diagnosis in all cases, the question, discussed later, being rather of its nature and causation.   Some slight cervical rigidity may also be present in cerebellar abscess but Kernig's sign is usually negative.   In spite, however, of these distinctions, lumbar puncture may be necessary before a definite opinion can be formed. One case of cerebellar abscess coming under our observation as a suspected case of cerebro-spinal fever may be mentioned :

CASE XLVIII.   Cerebellar Abscess.—The patient, aged 22, had had an ear discharge for several months, but with only an occasional headache and pain in the ear.   Two days before admission, the headache became very severe and he vomited several times.   On admission to hospital he was lethargic, lying listlessly in bed, mentally dull, slow in replying to questions, and complaining of continuous headache, chiefly vertical.   The temperature was 98·8° F., pulse 60, and respirations 20 per minute.   There was slight cervical rigidity, flexion of the head being somewhat limited, but the neck sign was definitely negative ; Kernig's sign was not present, although the hamstring muscles exhibited some slight rigidity, those on the right being a little more rigid than those on the left.   The plantar reflex was flexor but its demonstration produced active withdrawal of the leg.   The optic discs appeared normal ;   evidence of chronic otitis media with a perforation of the membrane was seen in the right ear ;   there was no definite evidence of mastoiditis.   Adiadokokinesia was absent, but the head showed a tendency to fall towards the side of the affected ear.   A blood cell count revealed 15,600 leucocytes per cubic millimetre.   Although the probable diagnosis was considered to be cerebral abscess, it was deemed advisable to perform lumbar puncture prior to advising exploration ; the cerebro-spinal fluid was quite clear and showed no increase in its cell content.   On exploration, *via* the mastoid antrum, a large cerebellar abscess was discovered.

If a cerebral abscess extends to the base of the brain and down the cord, or gives rise to a secondary meningitis, accurate diagnosis

from cerebro-spinal fever apart from lumbar puncture will be impossible. Bacteriological examination will then usually reveal the causative organism.

Cerebral Haemorrhage.—Meningitis, in older patients, may occasionally simulate cerebral haemorrhage. The following case is an example :

CASE XLIX.—The patient, aged 60 years, had had a cold with " sore throat " for about a week. Having complained of intense headache and vomiting one morning, he was waiting to report sick in the annexe to the medical hut, when, on his name being called, he was found quite unconscious. He was then sent to hospital and admitted with stertorous breathing as a case of cerebral haemorrhage ; there were no localising symptoms, but retention of urine was present. Next day he was not so deeply comatose, but was still unconscious, being stated to be very irritable and to insist on returning to lie on his side when moved on to the back ; it was quite impossible to rouse him. Owing to the presence of albumin in the urine and the complete absence of any localising symptoms, a diagnosis of uraemia was considered, but the microscopical examination of the urine failed to show any evidence of nephritis. On the following day (third day of illness) one of us was asked to see him and perform lumbar puncture. He was found irritable and resentful of interference, but there was apparently no delirium ; Kernig's sign was absent and neck rigidity only slight. Lumbar puncture, however, revealed a purulent cerebro-spinal fluid containing numerous meningococci both intracellular and extracellular.

Similarly, cerebral haemorrhage may occasionally resemble meningitis. As a rule, the age of the patient, presence of hemiplegia and absence of neck rigidity, Kernig's sign and pyrexia will give a clue to the diagnosis. If, however, the haemorrhage be basal, the clinical picture may closely simulate that of meningitis. The patient may then be stuporose or comatose and show general muscular rigidity, including cervical rigidity and a positive Kernig's sign. Fairley and Stewart describe one such case in which internal hydrocephalus, due to the obstruction of the foramina of Magendie and Luschka, was also present. In these cases lumbar puncture only will differentiate.

Meningeal haemorrhage will frequently give rise to a positive Kernig's sign, but the temperature is usually subnormal and neck rigidity absent.

Cerebral Thrombosis.—This condition rarely simulates cerebro-spinal meningitis. Apart from the syphilitic form, which is usually accompanied by hemiplegia or monoplegia, cerebral thrombosis

occurs in patients of an age at which cerebro-spinal fever is comparatively rare, viz. past middle age. Shortly after the reception, however, of the patient aged 60 mentioned above, the following case was met with, and will serve as an example in the differentiation of the condition :

CASE L. **Cerebral Thrombosis.**—The patient, aged 54, was admitted drowsy and incoherent in speech, with the history that on the previous day he had appeared quite well, but was found that morning in a semi-conscious state. On admission, the pupils were contracted, equal, and reacted slightly to light ; there was no strabismus. The limbs showed no paresis, the knee jerks were sluggish and the ankle jerks unobtainable. A definite extensor plantar reflex was elicited on the left side, while that on the right was flexor. There appeared to be some limitation in flexion at the neck, but no definite cervical rigidity ; Kernig's sign was negative. Incontinence of urine was present with slight albuminuria. The temperature was 98° F., the pulse-rate 66, and respirations 18. On lumbar puncture only 5 c.c. of cerebro-spinal fluid was obtained ; the fluid was slightly blood-stained, but showed no leucocytosis nor organisms. Left-sided hemiplegia gradually developed, and the patient died two days later. Post-mortem, thrombosis of the right anterior and middle cerebral arteries was found, with areas of softening in the region supplied by the obstructed vessels.

Acute Polioencephalitis and Poliomyelitis. (Heine-Medin disease).—Acute polioencephalitis and poliomyelitis sometimes present meningitic symptoms during the initial stages. The onset may be acute, with headache, vomiting, general pains, and a high temperature. Polioencephalitis, in which these symptoms are most frequently seen, is often ushered in by a convulsion, a frequent event in young children with cerebro-spinal fever. Further, the patient may be irritable and restless, and sometimes complain of pain in the neck and spine ; stupor may be present, but as a rule questions are answered fairly well. In the so-called meningitic form of the disease, described by Wickman, added to these symptoms, the neck and spine may show some rigidity and a certain degree of opisthotonus may even be present.

In polioencephalitis inferior, strabismus and other cranial nerve palsies may be observed comparatively early in the disease, but in poliomyelitis, paralyses affecting the extremities are not usually apparent before the fourth day or later. Herpes is not infrequent. Muscular rigidity, however, if present at all in a case of polioencephalitis or poliomyelitis, shows no tendency to increase as in cerebro-spinal fever ; Kernig's sign is not definite and, in

the initial stages, the pulse rate is raised in proportion to the temperature.

On lumbar puncture in the meningitic form of acute poliomyelitis, the cerebro-spinal fluid obtained, although under pressure, is clear to the naked eye ; on cytological examination a slight lymphocytosis may be found as well as a diminished glucose reaction.

According to E. Müller, the pyrexial stage of acute poliomyelitis is associated with a leucopenia, in contrast to the leucocytosis accompanying cerebro-spinal fever.

Lateral Sinus Thrombosis often gives rise to acute cerebral symptoms. The presence of an ear discharge, frequent rigors, and possibly local evidence of mastoiditis, together with the absence of any marked rigidity of the neck muscles and Kernig's sign, will usually serve to differentiate the condition from meningitis. One such case was admitted as a suspect. The patient had had an intermittent ear discharge for three years ; it had been continuous for the three months prior to admission. Headache, chiefly in the left temporal and frontal regions, had been present for three days, and for 24 hours he had experienced shivering attacks. On admission to hospital he was flushed and inclined to be excited, the temperature was 102° F. and pulse 120 per minute ; a foul ear discharge was found on the left side and slight tenderness, but no oedema, over the mastoid region ; neck rigidity was very slight but Kernig's sign was present. Two rigors were observed shortly after admission. Subsequent operation confirmed the diagnosis of lateral sinus thrombosis.

Cerebral Tumour is rarely mistaken for cerebro-spinal fever. The more or less gradual onset, absence of pyrexia, and often the presence of optic neuritis and localising signs serve to establish a diagnosis. In only one of our cases of cerebral tumour was lumbar puncture considered necessary to exclude the suspicion of meningitis. This was a patient, without localising symptoms, in whom subsequent post-mortem examination showed the presence of a large gumma in the left frontal lobe, wholly subcortical and extending as far backwards as the precentral gyrus.

Generalised Tetanus may sometimes be mistaken for cerebrospinal meningitis and *vice versa*. Features in common are the spinal and general muscular rigidity, occasional photophobia, and stiffness of the neck. In tetanus, however, the mind remains quite clear and trismus usually occurs prior to cervical rigidity ;

also the stiffness is at first confined to the neck and jaws.   Further, the frequent spasms and the history or presence of a wound are significant.   Trismus does occur, but indeed very rarely, in meningitis ; frequent spasms have also been described.   In our experience confusion between tetanus and meningitis is uncommon.   In a case seen by one of us, however, tetanus was suspected in a patient with a small, slightly septic wound in the supra-occipital region, apparently not involving the bone.   The symptoms were photophobia, rigidity of the posterior cervical muscles, and also of the masseters.   Kernig's sign was positive and lumbar puncture yielded a purulent fluid.

Infantile Convulsions.—As the onset of cerebro-spinal fever in young children is often accompanied by a convulsion, care must be taken not to mistake such a seizure for a convulsion due to dietetic or other causes.   Conversely, the appearance of such a symptom may give rise to a suspicion of commencing meningitis, especially if the convulsion is followed by a sharp rise in temperature.   Bulging of the anterior fontanelle, present during the seizures, disappears, however, during the intervals ; in meningitis, the bulging persists and the usual symptoms are also present.

Tetany.—In infants, differential diagnosis between tetany and acute meningitis may be difficult.   Chovstek's sign, also, is often present in the latter condition but Trousseau's sign is not usually obtainable.   The anterior fontanelle is not affected in tetany and neck rigidity is usually absent.   In some cases, however, it is necessary to perform lumbar puncture.

Epilepsy.—The convulsive seizure and resulting stupor may occasionally give rise to doubt, especially in children.   Horder, for instance, mentions the case of a child remaining in a state of epileptic stupor for four days, with raised temperature and doubtful Kernig's sign ; it was not possible to exclude meningitis without lumbar puncture.

Epileptiform seizures may occur in adults as well as in children during the early stage of cerebro-spinal fever ; the usual signs of meningitis, however, should serve to distinguish between the two conditions.   In our own experience, confusion of the two diseases rarely occurs.

Acute Mania is not often mistaken for cerebro-spinal fever but we have known the reverse occur in cases who were wildly delirious. If the fact be borne in mind that an apparently maniacal patient

may be suffering from early meningitis and proper examination be instituted, the mistake should never occur.

Delirium Tremens.—During a stage of excitement, cerebro-spinal fever may be mistaken for delirium tremens. Two cases of our series had previously been regarded as possibly suffering from the latter condition, one being an acute case and the other a subacute case with delirium and occasional excitement. Careful examination of the nervous system, however, revealed the true condition.

Migraine.—A patient, seen during the acute crisis of migraine, with intense headache and vomiting, might arouse the suspicion that the condition was in reality early meningitis, and more particularly if it were the variety with occasional strabismus (migraine ophthalmoplégique). The history of recurrent attacks, absence of mental symptoms, neck rigidity and Kernig's sign, will give the true diagnosis. The following case, however, was received as one of suspected cerebro-spinal fever :

CASE LI.—A man, aged 30, complained of intense headache, shivering attacks and vomiting ; shortly after admission he vomited several times. He was of a profoundly neuropathic temperament, of anaemic appearance, and complained of general muscular pains. There was no neck rigidity, Kernig's sign, or any organic abnormality of the nervous system ; shivering and shaking, of a hysterical character, occurred several times during the physical examination. The history was as follows : Since the age of 14 he had had similar attacks on an average of one per week. They were invariably accompanied by frontal headache, shivering attacks and finally vomiting. The duration of the attack was usually three days. Muscae volitantes were present throughout.

Hysteria.—Gowers, in his classical *Manual of Diseases of the Nervous System* (1888), refers to the occurrence of symptoms of meningitis in hysterical individuals during epidemics of cerebro-spinal fever, the exciting cause being fear of contracting the disease. Consequently, he termed the condition "meningitophobia." It is certainly true that hysteria may occasionally give rise to a suspicion of meningitis, and particularly if it complicates an attack of influenza or tonsillitis. The patient may lie completely apathetic, almost cataleptic, and take no notice of questions or of any attempts at rousing him. Response to painful stimuli is usually shown by the facial expression ; anaesthesia, however, suggested by the examination, may be demonstrated, even the corneal reflex being

absent. A case may show apparent neck rigidity, that is, firm resistance to any effort made at bringing the head forwards; similarly, resistance will be offered to extension of the leg on the thigh, giving rise to an apparent Kernig's sign. Difficulties are frequently increased owing to the fact that a history of onset is unobtainable from the patient, and that no notes may have been sent up to hospital with him. Perseverance, however, will usually show that there is no Kernig's sign and no real neck rigidity, unless the hysterical condition complicates influenza, when a slight increase in the relative tone of both groups of muscles may be found, although, as shown when discussing the differential diagnosis of influenza and meningitis, it seldom constitutes definite rigidity. If anaesthesia is not present, active withdrawal of the leg on plantar stimulation may also be found; the patient, however, seldom looks ill, and usually will take food readily. We have met with several cases; in two hysteria complicated influenza, and in one acute tonsillitis; of the former, one patient was so suspicious that lumbar puncture had to be performed in order to establish a positive diagnosis. Of other cases, the following is a remarkable example:

CASE LII. **Hysteria.**—A patient, aged 23 years, was admitted, without history, from a certain place situated at a considerable distance from the hospital. He appeared quite unconscious, with slow muttering " delirium," taking no notice of anything said to him, impossible to rouse, and lying on his side with eyes open. The pupils were equal and reacted normally to light; the conjunctivae could be touched with a scarcely perceptible reflex; there was no strabismus and the optic discs were normal. The tongue was slightly furred and the head showed some retraction as he lay in bed; on examination, however, the neck appeared only slightly rigid; he allowed the head to be brought forward some two or three inches past the vertical when an attempt was made at eliciting the " neck sign." Kernig's sign was absent, but the hamstrings were not fully relaxed; the limbs showed a certain amount of rigidity and even catatonia, that is, they remained for a considerable time in whatever position they were placed; the superficial and deep reflexes showed no definite abnormality; the heart and lungs were normal, and, further, he had incontinence of urine. The temperature, pulse and respirations were normal. Although the presence of catatonia strongly suggested a neurosis, it was considered desirable to perform lumbar puncture; the cerebro-spinal fluid was found to be quite clear, and showed no microscopical abnormality.

The patient remained in the above condition for about 14 days, taking his meals well when fed; strong faradism produced pain,

according to the change in facial expression, but failed to rouse him ; soap and water injected into the nostrils produced momentary resistance, the patient, however, again relapsing into his previous state. Finally, on improvement his mental condition appeared quite normal ; he answered questions well and intelligently, and always stated that he could not remember what had happened to him during his " illness."

A noteworthy case of hysteria simulating meningitis is also described by Bourke, Abrahams and Rowland. The patient—a young woman visiting her husband who had been ill with cerebrospinal fever for some weeks—suddenly developed headache, followed by a temperature of 101° F., pulse 68, retraction of the head, photophobia, ankle clonus and a double Kernig's sign. Lumbar puncture was performed three times and yielded a normal cerebrospinal fluid on each occasion. Recovery was rapid.

III. Miscellaneous Conditions

Other diseases with which, in our experience, cerebro-spinal meningitis has occasionally been confused are the following :

Gastro - enteritis. — The initial vomiting and prostration of cerebro-spinal fever may be mistaken for symptoms of gastroenteritis. Also, in infants, convulsions are by no means uncommon in disorders of the alimentary tract and " meningism " is occasionally met with. The anterior fontanelle, however, is depressed in gastro-enteritis, while in cerebro-spinal fever, although diarrhoea may occur at the onset, the fontanelle remains bulging and tense. In older children the rapid development of cervical rigidity and Kernig's sign should easily serve to differentiate the two conditions.

The following case illustrates well-marked meningism occurring in an infant in association with epidemic summer diarrhoea.

CASE LIII. **Epidemic Gastro - enteritis with Meningism.** — An infant, aged five months, was admitted to hospital with the history that diarrhoea had started suddenly ten days before ; 8-10 greenish and offensive motions had been passed per day, and vomiting had also occurred. The diarrhoea was of the lienteric type.

On admission the face was cyanosed, temperature 97·4° F. and pulse 140 ; the head showed marked occipital retraction, and partial opisthotonus was present. The pupils were contracted, but no strabismus was apparent. The legs were acutely flexed and the knee-jerks brisk. The fontanelle was almost closed, no bulging being present. On lumbar puncture the cerebro-spinal fluid was under no marked

tension, quite clear to the naked eye, and revealed no cytological increase ; cultures proved sterile.

The child died on the following day. On post-mortem examination no meningitis was present, the brain and meninges appearing normal.

Meningism may also occur in children with gastro-intestinal disorders other than epidemic diarrhoea. Such cases simulating meningitis have been described by O. Mayer and Mazzuoli. As with the case described above, in many instances positive diagnosis is only possible upon lumbar puncture.

Three of our adult patients suffering from cerebro-spinal fever had been regarded, prior to admission at the onset of the disease, as possible cases of gastro-enteritis. One had exhibited a somewhat sudden onset, accompanied by vomiting, following a boxing bout in which he stated that he received a comparatively slight blow ; the second had shown a gradual onset consisting of increasingly severe headache, epigastric and abdominal pain, and occasional vomiting. The third had felt suddenly ill with " shivering attacks " and headache, vomiting shortly after and again some hours later ; during the afternoon diarrhoea occurred. All three cases showed well-marked signs of meningitis on admission to our wards, on the third day of the disease in two cases and on the fourth in one.

Muscular " Rheumatism " (Muscular Fibrositis).—When this condition co-exists with pyrexia the differential diagnosis is the same as that for influenza. Subacute cases of cerebro-spinal fever with a gradual onset may at first be mistaken for cases of " muscular rheumatism," but the true diagnosis cannot remain long in doubt, as even if the temperature were normal when taken it would probably have risen a few hours later. Kernig's sign may appear to be positive in muscular fibrositis, but if passive extension and flexion at the knee be continued, it will usually prove to be absent, which is not the case in cerebro-spinal fever. Cervical rigidity may also appear to be present and the neck sign positive ; perseverance, however, will show that such stiffness is often voluntary, the patient being unwilling to relax the muscles owing to pain being produced on their being stretched. Further, in " muscular rheumatism " affecting the neck passive movement continued for a short time brings about considerable reduction in stiffness, while the reverse takes place in meningitis, the muscles becoming more rigid.

Five cases of " muscular rheumatism " were sent in as possible

cases of cerebro-spinal fever ; both were apyrexial and the diagnosis settled by attention to the above points. One case of cerebro-spinal fever subsequently coming under our care had previously been admitted to a general ward as influenza with severe " muscular rheumatism."

Uraemia. — Chronic nephritis with uraemic symptoms may occasionally give rise to a suspicion of meningitis. In uraemia the patient may be admitted comatose ; there may also be a history of headache and vomiting. Albumin is frequently found in the urine early in cerebro-spinal fever, but epithelial casts are rare. Kernig's sign, also, may be positive in uraemia, but neck rigidity is absent. In some cases differential diagnosis may only be possible on lumbar puncture, but as this procedure is the appropriate treatment for both conditions, doubt need not long be entertained. In uraemia the cerebro-spinal fluid is clear and will frequently be found increased both in pressure and amount obtainable.

The presence of albumin in the urine resulted in two cases of cerebro-spinal fever being admitted to hospital with the provisional diagnosis of uraemia. One case, received on the fourth day of illness, proved on examination to show well-marked signs of meningitis ; the second, aged 60, previously mentioned as having been found comatose, had been regarded as a possible case of uraemia after the diagnosis of cerebral haemorrhage was discarded.

Acute Osteo-myelitis of the Spine. — According to Grisel (quoted by H. D. Rolleston), acute osteo-myelitis of the vertebral column may sometimes be associated with meningitic symptoms. The fact that on lumbar puncture pus may be withdrawn from the extradural space, occasionally renders the diagnosis from meningitis very difficult. In two cases of osteo-myelitis of the spine mentioned by Rolleston there were no definite symptoms of cerebro-spinal fever, although pus was obtained on lumbar puncture. In one case admitted under our care, the first symptoms, following the development of acute pain in the lumbar region and pyrexia, were those of a lesion of the cauda equina. On examination, the characteristic anaesthesia and analgesia of the root type was found over the second and third sacral nerve areas on the left side and over the second sacral nerve area on the right, together with paresis of the left hamstring muscles, partial paresis of the right hamstrings, and retention of urine ; Kernig's sign was absent. Flexion at the neck was somewhat painful, but there was no definite rigidity of the cervical muscles. Acute tenderness was present on both

sides of the spine in the lumbar region, and within a day or two some swelling of the muscles was apparent. Incision gave exit to quantities of pus on both sides, but the case proved fatal. On post-mortem examination extensive necrosis of the second and third lumbar vertebrae was found, pus having extended into the vertebral canal, lumbar muscles and both psoas muscles, as well as into the kidneys.

Diabetes.—The diagnosis of impending diabetic coma had been considered, prior to admission, in one subacute case received by us on the ninth day of illness. Sugar had been found in the patient's urine on the fifth day, when he was complaining of intense headache and exhibiting nocturnal delirium. The presence of sugar in the urine of cerebro-spinal fever patients has previously been dealt with (p. 100).

Other conditions seen at different times as suspicious cases of cerebro-spinal fever proved to be (1) Muscular " rheumatism " with a drug rash (salicylate) accompanied by pyrexia; (2) calculus in the ureter complicated by pyrexia due to vaccination eight days before; (3) acute bronchitis with hysterical stupor; (4) delusional insanity with acute tonsillitis.

We met with one noteworthy case with cerebral symptoms of obscure origin, which at one time was regarded as a possible case of cerebro-spinal fever.

Case LIV.—A soldier, aged 26, was admitted to hospital unconscious, with the history that he was quite well until the morning of the previous day, when, on getting up, he complained of headache. He went on a short route march, but fell out after about a mile and returned to camp; later he was seen lying on his bed, not having taken any dinner. He appeared on evening parade but again fell out after marching less than a mile; he was told to report sick, but did not do so, and returned to his hut. The same evening he was found lying on his bed fully dressed; on being roused he arose and walked to the table, but from descriptions he was only partially conscious, unsteady on his feet, and apparently unable to speak; he was put to bed by his comrades and disturbed nobody during the night. Next morning he was found apparently unconscious, pale, pulse 84, and " was panting and gasping for breath "; his eyes were stated to be rolling from side to side and his limbs rigid. The man was then placed in a motor ambulance for conveyance to hospital, and regained sufficient consciousness to ask where he was going and to reply that he did not want to go into hospital as he was feeling better. On being admitted the same day as a transfer from the local hospital, the patient was

found to be quite unconscious, with the conjunctival reflex just present, breathing was quiet and not stertorous; he showed some cyanosis of the ears and feet; the temperature was 103° F., pulse 80 and respirations 80. There appeared to be slight cervical rigidity though not well marked; Kernig's sign was absent, the limbs all being flaccid; the pupils were equal, but reacted only sluggishly to light, and there was slight deviation of the right eye outwards. There was also a continuous tremor of the lower jaw of small range, and all the reflexes, both superficial and deep, were absent, excepting for a very reduced bilateral flexor plantar response. The urine contained neither albumin nor sugar, and the cerebro-spinal fluid showed no increase in the number of cells and proved sterile. A blood culture also proved negative. He died next day without change in condition, the temperature continuing between 103° and 104°, and the pulse rate, 80 during the morning, gradually increasing to 140.

Post mortem there was oedema of the meninges, but no pus or suggestion of meningitis. There was considerable oedema of the brain itself, the cerebral tissue being very sodden. The ventricles were not dilated and there was no flattening of the convolutions. The vessels were healthy and there was no skull fracture or other abnormality. The *heart* showed considerable dilatation of all its cavities, particularly the right, the cardiac muscle being soft and flabby owing to cloudy swelling. The valvular orifices showed some dilatation, together with hypertrophy of the right ventricle. The kidneys were rather large and showed advanced cloudy swelling, which might have suggested parenchymatous nephritis had albuminuria been present. Films of the serous exudate showed nothing abnormal and sections of the cortex and medulla showed no evidence of polioencephalitis.

IV. Other Forms of Meningitis

Meningitis, due to the various causative organisms, may produce symptoms clinically identical with those of cerebro-spinal fever.

Tuberculous Meningitis.—This condition in many cases can be diagnosed clinically. In contrast to that of cerebro-spinal fever, the onset is gradual and insidious, often lasting over a period of two weeks or longer, and being marked by a gradual failure in health, with headache developing slowly in intensity. It may be secondary to a known tuberculous lesion elsewhere, but such cases would seldom be suspected of meningococcal meningitis. The temperature is often only slightly raised and vomiting is less frequent than in cerebro-spinal fever. The mental condition is usually one of apathy or stupor rather than of active delirium. Photophobia is frequent as compared with its presence in cerebro-spinal fever;

unequal pupils and optic neuritis are also more often seen in tuberculous meningitis. Rigidity of the neck and Kernig's sign, if present, are as a rule moderate only and much less marked than in the meningococcal form.

On lumbar puncture, whereas the fluid withdrawn in cerebrospinal fever is more or less purulent with the exception of that obtained before the meninges are involved, in tuberculous meningitis it is only very slightly turbid or, especially in children, often clear to the naked eye. The protein content, however, is invariably increased and the globulin test positive. In contrast to the cerebrospinal fluid in meningococcal meningitis, besides the cells being relatively fewer, the lymphocytes as a rule predominate often up to 90 per cent. After long and patient search, tubercle bacilli may frequently be found in films of the centrifugalised deposit stained by the Ziehl-Neelsen method. Hemenway considers that the bacilli could be demonstrated in 98 per cent of cases ; although we have succeeded in finding them in the majority of cases suffering from this disease, the percentage does not reach this figure.

Occasional difficulty may be met with in a hydrocephalic case of cerebro-spinal fever coming under observation only late in the disease ; the fluid obtained by lumbar puncture may present an almost identical picture both microscopically and cytologically with that of tuberculous meningitis, the meningococcus not being found. Diagnosis may rest entirely on careful attention to the previous history and onset or the demonstration of tubercle bacilli in stained films.

Many cases of tuberculous meningitis have been admitted or seen in consultation by us as suspected cases of cerebro-spinal fever. In children diagnosis is not as a rule difficult, and one lumbar puncture usually confirms the opinion that the condition is tuberculous meningitis ; in adults, however, more difficulty may be experienced owing to its frequent resemblance to subacute cerebro-spinal fever.

Six adult patients, suffering from tuberculous meningitis, were admitted at different times as suspected cases of cerebro-spinal fever, their ages varying from 18 to 35 years. In five cases the onset was gradual and somewhat prolonged ; for instance, the patient had not felt well for four or five weeks, complaining of lassitude, headaches and occasional vomiting. In no case was a definite primary tuberculosis focus demonstrated, but one case, during the course, complained of occasional and severe abdominal

pain though without any very definite physical signs beyond general tenderness. Four cases were diagnosed as probably tuberculous prior to lumbar puncture ; two were not. On admission, cervical rigidity was present with different degrees of intensity in all cases, but in no patient so well marked as on the second or third day of cerebro-spinal fever ; in three cases only was Kernig's sign really definite, and it was not infrequently more marked on one side than on the other ; the remaining cases showed only slight rigidity of the hamstrings. Most of the patients were drowsy and apathetic on admission to hospital, the mental condition otherwise being normal ; progressive drowsiness was observed in all within one to five days, occasional muttering delirium being present in two. On lumbar puncture the cerebro-spinal fluid was slightly turbid in two, and in the others moderately clear, with the least suspicion of turbidity. One contained polymorphonuclear cells and lymphocytes in about equal proportion ; in the remainder lymphocytes predominated, and tubercle bacilli were demonstrated in three cases. In all cases the diagnosis was confirmed by autopsy.

The following is an example of tuberculous meningitis simulating cerebro-spinal fever :

CASE LV.—The patient, aged 35, was admitted to hospital complaining of a sore throat. The tonsils were somewhat inflamed, the temperature 101° F. and the pulse 100. Four days later the tonsillitis had improved, but the temperature had risen to 103° F. and the pulse had fallen to 84. On examination cervical rigidity was well marked, the neck sign being positive, but Kernig's sign was not definitely present ; the heart, lungs and abdomen appeared normal. No vomiting had occurred. On lumbar puncture, the cerebro-spinal fluid was found to be under moderate tension and showed the least possible trace of turbidity. Microscopically, polymorphonuclear and mononuclear cells were seen, the latter predominating, but no organisms were visible. Tubercle bacilli were not apparent in films specially stained. Muttering delirium ensued on the following day, but Kernig's sign did not become definitely positive until two further days had elapsed. At autopsy, a week later, well-marked tuberculous meningitis was found, together with small tubercles throughout the spleen and in the bronchial glands. No tubercles were apparent in the lungs or other viscera.

Pneumococcal Meningitis.—This form of meningitis frequently occurs as a primary condition, but is sometimes secondary to a focus of pneumococcal infection elsewhere—the middle ear, the accessory sinuses of the nose, the lungs—or forming part of a

pneumococcal septicaemia. It is not nearly so commonly seen secondary to pneumonia as is generally supposed, the number of cases probably being under 2 per cent. In the primary form an " influenzal " cold frequently precedes the onset of meningitis, which is as a rule somewhat sudden ; in those secondary to disease of the accessory sinuses of the nose and middle ear, the onset may be rather more gradual. Meningitis occurring during pneumonia is unlikely to be mistaken for cerebro-spinal fever. Although the development of serious symptoms is often much more rapid and the pulse rate relatively faster in pneumococcal meningitis than in the meningococcal form, positive diagnosis apart from the bacteriological examination of the cerebro-spinal fluid is impossible. On lumbar puncture a distinctly purulent fluid is almost invariably obtained in which Gram-positive cocci are as a rule easily found.

As an illustration the following case was admitted :

CASE LVI. **Pneumococcal Meningitis.** — The patient, aged 22, had complained of a " cold in the head " for two days, when severe headache suddenly appeared. On the following day vomiting occurred, and the same evening he became delirious and was stated to have frequent " fits." On admission, next morning, the patient was quite stuporose, but at times was extremely restless. The temperature was 102° F., pulse 140 and respirations 30 ; spasmodic twitching of the right arm occurred from time to time. Head retraction was pronounced and Kernig's sign positive ; the pupils were equal and no strabismus was apparent. Conjunctival injection was well marked. The tendon reflexes were slight and the abdominal reflexes absent. The heart, lungs, abdomen, ears and nose were apparently normal. On lumbar puncture 60 c.c. of purulent fluid were obtained under greatly increased pressure ; direct examination of the deposit showed numerous polymorphonuclear cells with Gram-positive lanceolate diplococci in considerable numbers. On culture, a pure growth of pneumococci was obtained.

The patient died on the following day, coma having supervened.

Four other examples of pneumococcal meningitis were also admitted as cases of cerebro-spinal fever. One was primary, no other lesion beyond meningitis being found at autopsy, and two others were secondary to otitis media and empyema of the sphenoidal sinus respectively ; the primary lesion in the latter was discovered only at post-mortem examination. In these three cases the diagnosis was made only as a result of the examination of the first sample of cerebro-spinal fluid withdrawn. The last case, described on page 337 (Case LVIII.), was a most unusual variety

of pneumococcal meningitis, no organisms being apparent until the 11th day of illness.

Streptococcal Meningitis is almost invariably secondary to infection elsewhere, usually penetrating wounds of the cranium, otitis media, etc. Meningitic symptoms occurring during the course of a known pyogenic infection will not usually be considered as possibly due to the meningococcus. If, however, such infection is in an obscure situation, as in the case described below, the case may be suspected as one of cerebro-spinal fever.

CASE LVII. **Streptococcal Meningitis.**—A man, aged 27, was admitted delirious, incoherent, with well marked carphology, twitching of the facial muscles and retention of urine. There was deviation of the right eye outwards and some rigidity of the neck, though not quite amounting to a definite " neck sign." The temperature was 101·8° F., and the pulse 120 ; Kernig's sign was well marked, and plantar stimulation showed a sluggish flexor response. The history obtained was that eighteen days earlier he had had submucous resection of the nasal septum performed, but no symptoms followed beyond slight congestion of the fauces, which disappeared in a few days. He was discharged from hospital eight days after the operation. Four days later he complained of intense headache and anorexia, both of which persisted, but he did not take to his bed until the third day of these symptoms ; his temperature was then said to be 104° F. For the ensuing 48 hours he appeared rather better, but later delirium and restlessness supervened and he was sent into hospital.

On admission, the site of the operation was quite dry and healed, but on lumbar puncture a purulent fluid was obtained, containing numerous pus cells and abundant streptococci almost wholly extracellular. On culture a pure growth of streptococci was obtained. The organisms were also cultivated from the blood stream.

The patient was treated with anti-streptococcal serum (in 30 c.c. doses) both intrathecally and intravenously ; he was also given 100 c.c. of eusol intravenously. Nasal irrigation with eusol was also employed. The intrathecal injections were made daily after the evacuation of as much pus as possible ; following the first two doses, great difficulty was experienced in administering the serum owing to the extremely slow inflow. The patient died during the night of the fourth day in hospital. Streptococci persisted both in films and cultures of the cerebro-spinal fluid throughout the course of disease. Post mortem, well marked meningitis was present ; pus was also found in the sphenoidal sinus and posterior ethmoidal cells, and could be traced to the roof of the naso-pharynx. In marked contrast to meningococcal meningitis, the spleen was much enlarged, being over twice the normal size. Streptococci were present in films both from the bony sinuses and meninges.

In another case of meningitis reported by one of us (C. W. D.), fusiform bacilli were associated with streptococci.

Staphylococcal Meningitis is a rare but rapidly fatal disease; it can only be diagnosed bacteriologically.

Anthrax Meningitis. — Acute anthrax may occasionally be mistaken for cerebro-spinal fever. The onset may be somewhat similar to that of the latter disease, consisting of malaise, headache and "chilliness"; vomiting, if present, usually appears late. Drowsiness, delirium, and, finally, coma eventually supervene and there may be twitching of the limbs. Muscular rigidity, giving rise to cervical rigidity and a positive Kernig's sign, may also occur. Such meningitic symptoms are due to the fact that in generalised anthrax the B. anthracis is invariably found in the cerebral and meningeal vessels, and often produces haemorrhagic extravasation into the subarachnoid space. R. J. Reece has recently reported five cases of acute anthrax primarily thought to be cerebro-spinal fever; in three cases no external skin lesion was evident.

In doubtful cases, especially in the absence of an external lesion, diagnosis can only be made on lumbar puncture, when a haemorrhagic fluid is obtained containing B. anthracis.

Acute Syphilitic Meningitis.—Acute syphilitic meningitis, occurring during the secondary stage and developing with or soon after the cutaneous eruption, may occasionally be mistaken for cerebro-spinal fever. The condition is rare but several cases have been recorded in which, 1-3 months after the initial syphilitic lesion, the patient has developed all the signs of an acute meningitis— pyrexia, vomiting, neck rigidity, Kernig's sign and strabismus. In a few cases the onset has been quite sudden, being accompanied by headache and vomiting.

On lumbar puncture the cerebro-spinal fluid usually is clear to the naked eye, but on microscopical examination shows a well-marked lymphocytosis; a few polymorphonuclears are occasionally present. Both the blood and cerebro-spinal fluid give a positive Wassermann reaction.

Owing to the presence of numerous lymphocytes in the cerebro-spinal fluid, and also to the fact that cases may exhibit a gradual onset, the condition is more liable to be mistaken for tuberculous meningitis than cerebro-spinal fever. S. A. K. Wilson and A. C. E. Gray, however, record a case of syphilitic meningitis occurring in a man aged 24, who was admitted to hospital and for six days

treated as a case of cerebro-spinal fever. The first sample of cerebro-spinal fluid withdrawn showed excess of lymphocytes and a few polymorphonuclear cells, but no organisms. Later, both the blood and the cerebro-spinal fluid gave a strongly positive Wassermann reaction. An instructive review of the literature of syphilitic meningitis is also given in the report.

In a case of meningitis with a recent history of syphilis and showing no response to treatment with anti-meningococcal serum, especially if lymphocytes predominate in the cerebro-spinal fluid, syphilitic meningitis should be considered and a Wassermann reaction performed on the cerebro-spinal fluid and blood serum. Further points, according to Brenstein, are that the ordinary meningeal symptoms are often undeveloped, and little change in respiration or pulse rate occurs.

Meningitis due to various other Organisms.—Of other forms of meningitis, those due to the Bacillus influenzae and Bacillus coli communis may also be met with. Meningitis due to Friedländer's bacillus and Gaertner's bacillus has also been described. Quite recently, the occurrence of meningitis due to infection by the Spirochaeta icterohaemorrhagicae without the symptom of jaundice has been reported. Such conditions can only be identified bacteriologically.

The occurrence of gonococcal meningitis is doubtful; an instance of meningitis, however, said to be due to the gonococcus, was published in 1907 by D. Bieck: A man, aged 48, who had been suffering from a chronic urethral discharge for a year, developed a fresh discharge, and after six days became delirious and maniacal; coma and death followed shortly afterwards. At autopsy, patches of purulent exudate were found in the cerebral meninges, the microscopical examination of which, according to G. Luys who quotes the case, revealed the gonococcus. The diagnosis of gonococcal meningitis must, of course, only be accepted with the utmost caution, owing to the difficulty of distinguishing the gonococcus from the meningococcus.

That meningitis can be caused by the micrococcus flavus is shown by a case recently recorded by Teacher and Kennedy. The patient, a man aged 50, was admitted to hospital on account of head injuries caused by a fall of coal; the nose was broken, there was bruising about both eyes and the chin, and a large scalp wound was present in the upper occipital region. Two days later, symptoms of meningitis developed, death occurring on the fifth day. Post-

mortem examination revealed a fracture of the cribriform plate
of the ethmoid and extending across the right orbital plate, together
with well-marked purulent meningitis. Films made from the
purulent meningeal exudate revealed Gram-negative cocci, which
cultural appearance and fermentation reactions proved to be
micrococcus flavus.

Several of the cases in our series, on admission to hospital, showed
evidence of an ear discharge due to otitis media of long standing.
Clinically, in all cases, meningitis was the obvious diagnosis, the
question being rather one of differentiation between cerebro-spinal
fever and meningitis secondary to the ear condition. In cases
that were mild or of only moderate severity, bearing in mind that
meningitis of otitic origin is usually extremely severe, cerebro-
spinal fever was considered the most likely diagnosis. Lumbar
puncture usually revealed a turbid fluid in which meningococci
were easily identified. In one case, however, they were not identified
until the third specimen of cerebro-spinal fluid was examined, but
for reasons set forth in the following paragraph, treatment with
anti-meningococcal serum had already been instituted and the
patient recovered.

Owing to the paramount importance of early serum administra-
tion in the treatment of cerebro-spinal fever, it has invariably been
our practice to give anti-meningococcal serum to a suspected case
of cerebro-spinal fever without waiting for the bacteriological
examination, if, on lumbar puncture, the cerebro-spinal fluid proves
to be turbid. As meningococcal meningitis is the only form of
meningitis with a relatively good prognosis, no harm can be done
to a possible tuberculous, pneumococcal or streptococcal case by
this procedure, and it may be of inestimable benefit in one of
cerebro - spinal fever. Therefore anti - meningococcal serum was
given at the outset in the case mentioned above, the administration
being amply justified later.

Two cases of our series failed to show the presence of the meningo-
coccus in the cerebro-spinal fluid or naso-pharynx throughout the
course of meningitis. Of these, one—a subacute case—was not
received until the 13th day of his illness; he eventually recovered
after a course of about 46 days in all, being treated with daily
intrathecal injections of anti - meningococcal serum until the
symptoms had definitely improved; lumbar puncture was then
continued daily until the cerebro-spinal fluid was clear to the naked
eye. The second case was very acute, being received unconscious

on the second day ; he also recovered under the same treatment after a short course of ten days.

As meningococcal meningitis, with the exception of extremely rare cases, is the only variety of meningitis that recovers, we have regarded these cases as examples of cerebro-spinal fever. Further, both cases responded well to anti-meningococcal serum, and with the acute case the response was particularly rapid.

Subacute cases of meningitis, however, in which no organisms are at first visible, are not invariably due to the meningococcus. The following case is noteworthy, as, although remaining subacute for some days, it eventually proved to be one of pneumococcal meningitis, but occasioned considerable difficulty as regards accurate diagnosis.

CASE LVIII.—The patient, aged 11 years, had complained of headache and seemed generally unwell ; three days later he vomited and became somewhat drowsy. For four days following this, his condition remained about the same, the temperature remitting between 101° F. and 104° F. When seen by one of us on the fifth day, his mental condition was quite normal, slight photophobia was present, neck rigidity moderate and Kernig's sign positive ; the sphincters were unaffected. The heart, lungs, ears and nose showed no abnormality. On lumbar puncture a slightly turbid fluid under moderate pressure was obtained. The diagnosis was then considered to lie between tuberculous and meningococcal meningitis, with the evidence slightly in favour of the former. According to the principle enunciated above, that no harm can be done to a tuberculous case while one of cerebro-spinal fever will benefit considerably, anti-meningococcal serum was administered. Direct microscopical examination of films of the centrifugalised deposit of the cerebro-spinal fluid showed the presence of numerous polymorphonuclear cells but no organisms, even after prolonged and repeated search. Similarly, no tubercle bacilli could be demonstrated. This additional evidence, therefore, rather suggested cerebro-spinal fever, but a naso-pharyngeal swab was negative. Lumbar puncture and serum administration was continued daily, but his condition showed little or no alteration, either in the clinical signs or in the microscopical characters of the cerebro-spinal fluid, until the 11th day of illness. Muscular rigidity was then more marked, and during the evening the patient became delirious and incontinent for the first time. Lumbar puncture, next day, revealed a purulent fluid, which on microscopical examination showed numerous Gram-positive lanceolate diplococci. Delirium and restlessness increased, floccitation and carphology appeared and, two days later, the case terminated fatally.

CEREBRO-SPINAL fever occasionally occurs during the course of other microbial diseases and, *vice versa*, other infections may occur during the course of cerebro-spinal fever.

Typhoid Fever.—Sophian describes a case of typhoid fever in which a meningococcal meningitis developed towards the end of the second week. The patient, a boy aged nine years, was admitted to hospital with an indefinite history of about ten days' illness. He exhibited all the usual signs of meningitis together with a high temperature ; the pulse was 120, respirations 24 and somewhat irregular. Consciousness was quite clear, but the patient was hyperaesthetic and irritable. Lumbar puncture yielded a turbid fluid containing meningococci ; the same organism was obtained from the naso-pharynx. After four intrathecal doses of anti-meningococcal serum, the cerebro-spinal fluid became clear, cells and organisms being absent ; also, the meningeal symptoms improved, neck rigidity and Kernig's sign disappearing. The pyrexia during the first week had continued between 103° F. and 104° F. ; in spite, however, of the apparent disappearance of meningitis, the patient continued to exhibit considerable pyrexia which had now become somewhat remittent, varying between 101° and 104° F. The abdomen was distended, and he complained of occasional pain in the right iliac fossa, as well as considerable tenderness. The spleen was slightly enlarged and the pulse slow and dicrotic. A Widal reaction proved positive in high dilution. After a further week the temperature reached normal.

The attack of cerebro-spinal fever was comparatively mild and the pyrexial course throughout rather that of typhoid fever ;

the latter condition did not appear to be at all influenced by the meningitis.

Paratyphoid Fever.—A case of cerebro-spinal fever developing paratyphoid A fever is recorded by E. Parry Evans. The patient, aged 21, was admitted to hospital with a temperature of 101·2° F., pulse 100, retracted head and a positive Kernig's sign. The onset had occurred four days previously, with malaise, nausea and later vomiting. Beyond the fact that the patient was somewhat drowsy and lachrymose, the mental condition was fairly normal. On lumbar puncture a clear fluid was obtained which, on microscopical examination, showed Gram-negative diplococci and yielded meningococci in culture. Six days later the meningitis had improved considerably, and muscular rigidity was much less marked. About this time, however, the patient developed signs suspicious of typhoid fever — continued pyrexia, roseolar rash and palpable spleen. On blood culture, Bacillus paratyphosus A was isolated. For three weeks the patient then ran an uneventful course of paratyphoid A fever of no more than usual severity ; following this, symptoms of an acute abdominal condition developed, which laparotomy showed to be due to a hernia of the small intestine through a breach in the mesentery. Eventually the patient made a good recovery.

Of our own cases of cerebro-spinal fever, one developed an attack of paratyphoid B fever early in convalescence from a mild attack of the former disease. The patient, a soldier, aged 18, was admitted to hospital on the second day of illness in a delirious condition and exhibiting the characteristic signs of meningitis ; lumbar puncture yielded a turbid fluid containing meningococci. On each of the first four days in hospital, 30 c.c. of anti-meningococcal serum were given intrathecally and lumbar puncture then repeated daily until a cerebro-spinal fluid clear to the naked eye was withdrawn—on the seventh day of illness. The temperature by this time had reached the normal level, and beyond a slight rise of temperature accompanying a serum rash on the tenth day of illness, no further pyrexia occurred. A few weeks later the patient complained of headache and abdominal pain ; these symptoms were followed by diarrhoea of 48 hours' duration. On examination, the temperature was found to be 102° F., pulse 100 and respirations 25. There was some abdominal tenderness to the right of the umbilicus, but no rigidity ; the neck muscles were perfectly supple and Kernig's sign absent. A blood count showed

the presence of 13,000 leucocytes per c.c. and on culture the blood yielded Bacillus paratyphosus B. The course of illness continued for nine days, the pyrexia being of a remittent type between 99° and 101° F. After the first three days the pulse rate did not reach above 90 per minute and at no time were any "rose spots" observed nor was the spleen palpable. The patient, being a recruit at the time he developed cerebro-spinal fever, had not then received the usual inoculation against typhoid and paratyphoid.

Measles.— Cerebro - spinal fever often follows closely upon recovery from rubella and measles ; the co-existence of either of these conditions with cerebro-spinal fever would, of course, be difficult to prove.

Secondary Infections of the Meninges.—In rare instances other pathogenic organisms may co-exist with the meningococcus in the meninges, or secondary meningitis due to invasion by a different organism may occur.

Influenzal Meningitis.—Sophian mentions a case of cerebrospinal fever, occurring in New York, during the acute stage of which an influenzal meningitis developed. Both the meningococcus and the Bacillus influenza were isolated from the cerebro-spinal fluid.

Pneumococcal Meningitis.—A number of cases of cerebro-spinal fever have from time to time been reported as exhibiting pneumococci in the cerebro-spinal fluid as well as meningococci.

According to Sophian, some instances of cerebro-spinal fever developing a secondary pneumococcal meningitis were observed during the Texas epidemic of 1912. W. J. Wilson, R. B. Purce and G. Darling mention two cases of cerebro-spinal fever in which the meningococcus was accompanied by the pneumococcus. One case proved fatal and the other made a good recovery ; in the latter case the pneumococcus was said to be the primary infecting agent since it was the organism first found in the cerebro-spinal fluid. Notes of the examinations are reported as follows :

July 14.	Fluid turbid.	Lanceolate Gram-positive diplococci.
,, 16.	,, ,,	A few lanceolate Gram-positive diplococci.
,, 20.	,, ,,	Gram-negative meningococci ; no pneumococci.
,, 21.	,, clear.	

In the second case both organisms are said to have been found

at the same time. No mention, however, is made of the cultivation of either organism.

In the earlier part of 1917 Netter and Salanier, of 300 cases of cerebro-spinal fever, reported four as developing a secondary pneumococcal infection. In a more recent communication the same observers tabulate 23 cases of secondary pneumococcal meningitis occurring during the course of cerebro-spinal fever. H. D. Rolleston also mentions two cases of mixed meningococcal and pneumococcal infection of the meninges ; in one case both organisms were detected in the first sample of cerebro-spinal fluid withdrawn, the patient recovering. In the second instance, pneumococci were discovered only at autopsy, the case proving fatal on the 11th day.

As a general rule, the pneumococcal infection occurs relatively late in the course of cerebro-spinal fever and even when recovery appears to have taken place. In most cases no primary pneumococcal focus is apparent, and infection is presumed to have occurred from the naso-pharynx, diminished resistance favouring such an occurrence. Long-standing cases of hydrocephalus following cerebro-spinal fever occasionally develop a secondary pneumococcal infection of the cerebro-spinal fluid.

In considering such secondary pneumococcal invasions, it is found that some of the reports are based merely upon the stained appearance of films of the cerebro-spinal fluid, without confirmation by culture or fermentation reactions. Culture of the organisms, however, is essential before one can accept as proven the existence of a double infection. In some cases of pneumococcal meningitis we have ourselves found that the pneumococci in the cerebro-spinal fluid retain the Gram-stain poorly and sometimes even appear Gram-negative ; the cultural characteristics, however, are unchanged.

Streptococcal Meningitis.—Of a series of 247 cases of cerebro-spinal fever occurring in the Royal Navy from August 1914 to August 1917, H. D. Rolleston mentions three as developing a secondary streptococcal meningitis. In one case the second lumbar puncture yielded a fluid containing streptococci as well as meningococci, the latter organisms having been obtained in pure culture from the first cerebro-spinal fluid withdrawn. In the second case the streptococcal meningitis was of otitic origin, and in the last case invasion occurred *via* the lumbar puncture wound.

Tuberculous Meningitis.—A number of observers—Holdheim,

Hübner, Hunter and Nuttall, Lenhartz, Frohman and Netter—have reported instances of tuberculous meningitis in which an organism believed to be the meningococcus was isolated from the cerebro-spinal fluid. In some of the cases, however, the meningococcus was not found in the original films examined but appeared later in culture. According to Sophian, the cultural characters of the organism isolated in most instances did not coincide with those of the meningococcus, a fact which naturally leads to the suspicion of secondary contamination of the cerebro-spinal fluid examined.

H. D. Rolleston mentions a case of cerebro-spinal fever the onset of which was followed by a rash becoming haemorrhagic ; the case proved fatal on the 18th day, and on post-mortem examination an additional tuberculous infection of the meninges was found.

Flack also describes a case as being possibly one of mild cerebro-spinal fever supervening on tuberculous meningitis. The cerebro-spinal fluid remained persistently clear, and although at first Gram-negative cocci were found microscopically, no growth of the meningococci was obtained from the cerebro-spinal fluid or naso-pharynx. Appearances in stained films, however, are often deceptive. One case, aged 19 years, admitted under our care and suffering from acute meningitis, had the clinical appearance of cerebro-spinal fever. On lumbar puncture the cerebro-spinal fluid was turbid, and on microscopical examination the cytological characters were practically identical with those of cerebro-spinal fever. No tubercle bacilli or other organisms, however, could be found, but one or two granules taking up the counter-stain (carbol-fuchsin) were seen in the film ; they were not meningococci although they might easily have been mistaken for such. These granules were seen at the first examination only. Culture tubes remained sterile throughout. The patient died within a week, and, on post-mortem examination, proved to be a case of acute tuberculous meningitis associated with generalised miliary tuberculosis.

Although cases undoubtedly do occur, the apparent association of meningococcal and tuberculous meningitis is often deceptive. In an analysis of reported instances of this rare combination, Beriel and Durand accepted 8 cases only. Elser and Huntoon examined a series of 25 cases of tuberculous meningitis and failed to find any organism other than the tubercle bacillus. Libman examined 44 with a similar result. Sophian investigated the cerebro-spinal fluids of over 200 cases of tuberculous meningitis

and found no instance of mixed meningococcal infection. Of a large number of patients suffering from tuberculous meningitis met with in civil practice as well as in 20 military cases, we have met with no example of primary or secondary meningococcal meningitis.

CHAPTER XIV

LESIONS DUE TO THE MENINGOCOCCUS OTHER THAN THOSE
WHICH ARE ASSOCIATED WITH MENINGITIS

Meningococcal Septicaemia.—Cases occasionally occur in which the meningococcus reaches the blood stream and there persists and multiplies, causing a true meningococcal septicaemia with no subsequent meningitis.

The onset is usually sudden but may sometimes be preceded by a short period of malaise; vomiting may or may not occur. At first the temperature is often subnormal and associated with symptoms of collapse; later, however, it rises, especially towards death. The pulse is rapid, feeble and not infrequently imperceptible; respiration is always rapid. Pain in the back and limbs may also be complained of. A characteristic feature is the presence of a purpuric eruption, often distributed all over the body, the face not escaping; almost invariably, however, the spots on the lower part of the trunk and the legs are the most marked. Neck rigidity, spinal rigidity and Kernig's sign are all absent. On lumbar puncture a clear and sterile cerebro-spinal fluid is obtained, usually under no tension. On blood culture meningococci are obtained and intracellular diplococci may sometimes also be seen on examination of stained blood films.

Post mortem, the usual signs of general sepsis are found; petechial haemorrhages affecting the mucous membrane of the stomach appear to be a well-marked feature.

One of the earliest recorded cases of meningococcal septicaemia was reported by Andrewes in 1906. The patient, a medical man, was attacked with severe symptoms of general sepsis, including the appearance of a purpuric eruption; death occurred within a few days. Blood films taken from the median basilic vein shortly

before death showed pairs or small groups of cocci in the poly-morphonuclear leucocytes. Blood culture yielded meningococci. No signs of meningitis were detected during life, and at autopsy there was no evidence of meningitis, even on microscopical examina-tion.

Pybus reports the case of a girl, aged three years, who was seized with sudden abdominal pain and vomiting. When seen seven hours later, the temperature was found to have risen to 103° F.; the abdomen presented no abnormal signs beyond a readily palp-able liver edge, but petechial and small haemorrhagic patches were present over the lower extremities ; no signs of meningitis were apparent. The patient died three hours later, that is, after a total course of less than 13 hours. At post-mortem examination no signs of meningitis were present ; the liver was unusually red in colour and petechiae were visible in the mucous membrane of the stomach. Cultures from the heart blood yielded a pure growth of meningococci.

W. P. Herringham, as a consulting physician to the British Expeditionary Force in France, had the following cases reported to him : W. Anderson had charge of the case of a man admitted to a casualty station with a subnormal temperature and exhibiting abundant râles in the lungs ; the history of onset was not known. On the following morning a purpuric rash developed, chiefly affect-ing the extensor aspects of both legs and thighs. By 11 P.M. on the same day the pulmonary signs were considerably worse and the patient was unconscious ; he died on the following day (Fig. 40). Five c.c. of blood withdrawn prior to death by McNee, and incubated in 30 c.c. of bouillon, after three days' incubation yielded a Gram-negative diplococcus ; the organism showed the fermentation reactions of the meningococcus and corresponded to the Type II. (Gordon) coccus.

McDonnell's case had been admitted to a field ambulance, with a temperature of 104° F., symptoms of collapse, and with history of severe pain in the back, frontal headache, and finally vomiting (Fig. 41). On admission to the casualty station there was no sign of meningitis, respiration was rapid, but both the chest and abdomen appeared normal ; scattered over the trunk and limbs, however, was a marked haemorrhagic rash, which the patient stated had been present for two days. The purpuric eruption was most intense over the lower limbs. Lumbar puncture revealed a perfectly clear and sterile cerebro-spinal fluid under no

increased pressure. A. C. H. Gray, however, obtained meningo-
cocci on blood culture after 48 hours' incubation; the coccus
corresponded with Gordon's Type II. On the following day the
patient became delirious and very restless, and died during the
night. Post-mortem examination showed the following: The
spleen was large and soft, petechiae were present over the surface
of the heart and particularly in the mucous membrane of the cardiac
end of the stomach; the upper part of the duodenum was also
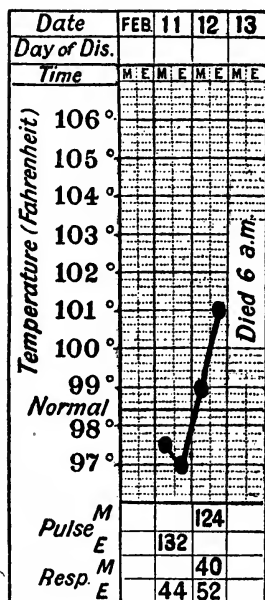
Fig. 40.—Meningococcal Septi-
caemia (after Anderson,
McNee and Herringham).
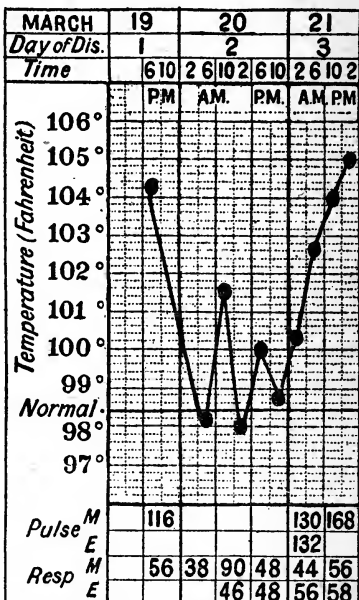
Fig. 41.—Meningococcal Septicaemia (after
McDonnell, Gray and Herringham).

affected. No meningitis was present, and beyond congestion
nothing noteworthy was seen in the other organs; meningococci
were also cultivated from the spleen.

The case reported by F. C. Davidson was admitted to hospital
with a temperature of 104·6° F., pulse 112, and respirations 56.
The following history was obtained: The patient, having complained
of nasal catarrh for three days, developed an urticarial rash; after
four days' absence, however, he returned to his duties, but on the
following day again felt unwell, complaining of a sore throat and
headache. On the day after his admission to hospital, the patient

developed a purpuric rash of practically universal distribution ; the larger spots, however, appeared over the lower extremities. There were no signs of meningitis, but he was drowsy, cyanosed and complained of considerable pain in the limbs. Lumbar puncture yielded a clear and sterile fluid under no tension. In blood films, however, Gray found many leucocytes containing intracellular Gram-negative diplococci ; cultures of the blood showed, after 36 hours, typical meningococci which A. W. M. Ellis identified as corresponding to Type II. organism. The patient died on the day following the appearance of the purpuric rash.

Another case is mentioned by Herringham in which both the clinical and post-mortem appearances closely resembled that of the above case, including the presence of a purpuric rash. Blood culture was not performed during life and that of the heart blood at autopsy proved sterile.

The presence of a septicaemia preceding meningitis (Case II. p. 63), and a septicaemia occurring with meningitis in fulminating types of the disease are dealt with elsewhere (Chapters V. and VII., and pp. 62 and 137).

Ulcerative Endocarditis.—Cases in which ulcerative endocarditis develops as a complication of cerebro-spinal fever are occasionally met with and have already been mentioned (*vide* p. 182). Endocarditis associated with meningococcal septicaemia in the complete absence of meningitis is, however, exceedingly rare.

The following case, recently under our care, is an example of this condition. No physical signs of meningitis were present at any stage of the disease, and at the autopsy meningitis was found to be absent.

CASE LIX. (Fig. 42) **Meningococcal Septicaemia with Ulcerative Endocarditis.**—The patient, a man aged 37, was received into hospital, the temperature being 104° F., with a provisional diagnosis of influenza. He was said to have had " rheumatic fever " when young, but to his knowledge had had no other illnesses. On admission no definite physical signs were apparent, and after five days the temperature fell to normal, the patient being allowed up a day or two later. The pulse rate, at this time, varied between 84 and 90 per minute ; during the pyrexial period it had averaged 106. When he had been up about six days, he was suddenly seized with rigors, the temperature rose to 100° F., and from this time he complained of dyspnoea and frequent palpitation.

General Course.—The pyrexia occupied six days before reaching its maximum (103·4°), having gradually risen from 100° by successively
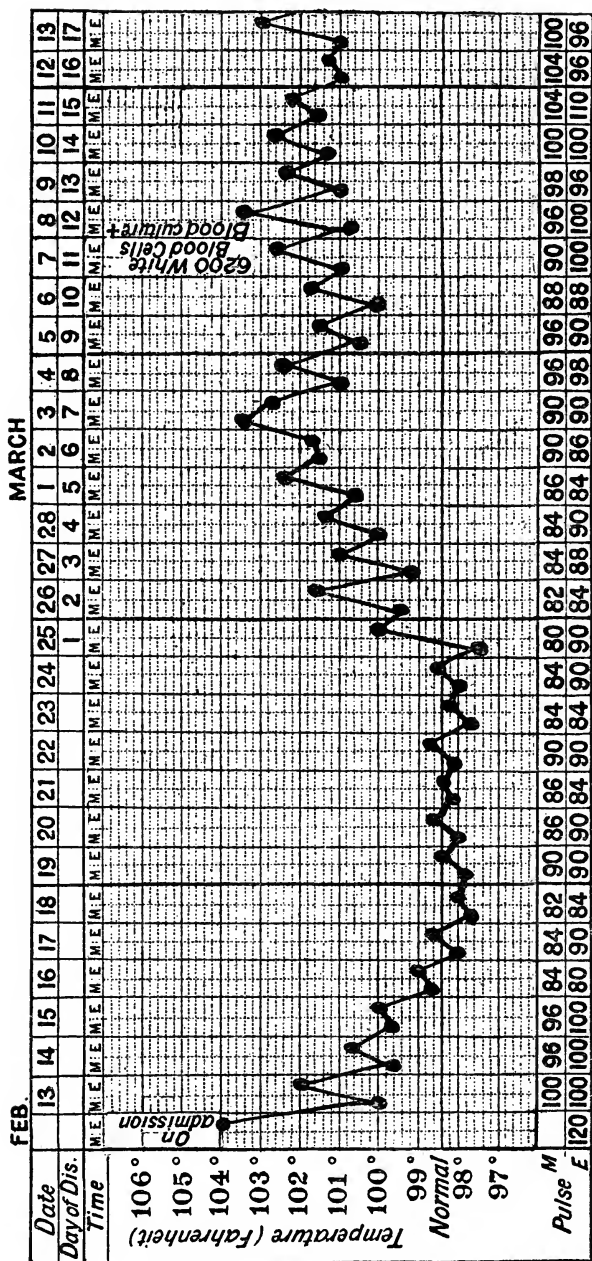
Fig. 42.—Meningococcal Septicaemia with Endocarditis. (Case LIX. p. 347.)

Fig. 42*.—Meningococcal Septicaemia with Endocarditis.   (Case LIX. p. 347.)
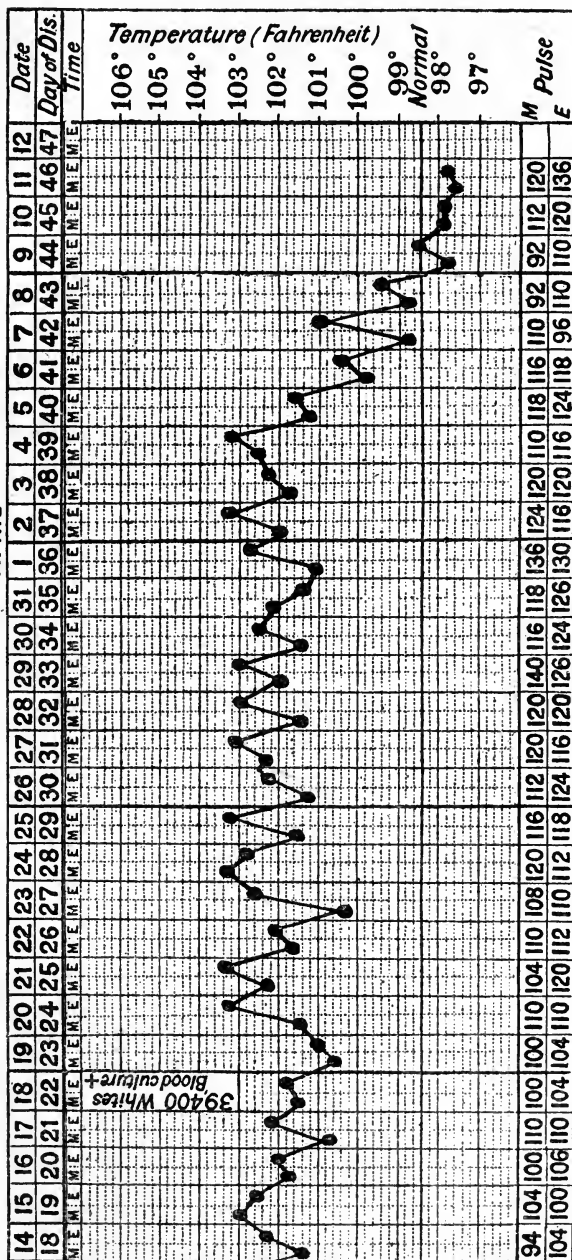
increasing evening rises, the morning remissions being 1°-2° lower. From this point onwards the pyrexia was rather of a continued type, varying between 100° and 103·4° during the second week, but not falling below 101°, excepting on a few occasions, during the course of the third, fourth and fifth weeks ; the morning temperature was usually about one degree lower than that in the evening. Throughout these periods the patient complained of more or less constant dyspnoea, occasionally showing exacerbations in severity. During the fourth and fifth weeks, he was somewhat cyanosed and the tongue was dry and tremulous. Towards the end of the sixth week his condition became increasingly grave, oedema of the lower extremities made its appearance and the temperature began to fall ; it did not rise above 99·4° during the four days preceding his death, which occurred after a course of six and a half weeks.

No rash or petechiae ever appeared, nor was there any evidence of meningitis ; both neck rigidity and Kernig's sign were absent throughout the course and the mental condition, excepting when he sank into unconsciousness before death, was invariably normal.

Circulatory System.—*Heart.*—During the first three weeks of the illness a " to and fro " murmur could be heard at the base of the heart in the aortic region, together with a very faint systolic murmur at the apex. The heart became moderately enlarged, the apex beat reaching just outside the nipple line in the fifth interspace. By the end of the fifth week, however, the enlargement was considerable ; the apex extended in the sixth interspace fully one and a half inches beyond the nipple. There was a marked double aortic murmur which varied in intensity from time to time ; the apical systolic murmur also became more pronounced. During the last week of the course the cardiac beats were indistinct and the murmurs occasionally inaudible.

Pulse.—The pulse rate did not reach above 90 per minute during the first week ; up till the end of the third week its highest recorded rate was 104, the average for this period being about 100. Thereafter, however, it seldom fell below 112 and was frequently 136, especially during the fifth week. With the decline of the pyrexia the pulse rate also showed a tendency to fall, rising again, nevertheless, before death.

Blood.— A count of the white blood cells midway through the second week showed only 6200 per c.mm. At the same time the patient's serum failed to agglutinate paratyphoid A, B, or typhoid bacilli ; a Wassermann reaction also was negative. Blood culture (10 c.c. of blood in broth), however, yielded a Gram-negative diplococcus, showing the cultural characteristics and fermentation reactions of the meningococcus—it fermented glucose and maltose but not saccharose. The organism, moreover, gave a positive agglutination reaction with Gordon's Type II. univalent meningococcal serum, but not with that of the other three types.

Early in the fourth week the leucocytes had increased to 39,400 per c.mm., and, to confirm the previous findings, another blood culture

was taken with the same result as before—the isolation of a Type II. meningococcus.

Other Viscera.—At the beginning of the fourth week the spleen appeared to be tender, and although enlarged to percussion during the sixth week, its edge was never definitely palpable. The liver was found to be enlarged as early as the third week, the lower edge extending about 1-1½ inches below the costal margin. The lungs always appeared clear, but a scanty mucoid expectoration occurred throughout. The urine, whenever examined, contained a trace of albumin.

Autopsy.—*Brain.*—Pale and anaemic but otherwise normal. No meningitis.

Heart.—The heart was large and soft, being 18½ ounces in weight. The cardiac muscle generally, and particularly that of the ventricles, showed well-marked myocarditis (musculature mottled, small pale areas alternating with congested areas, and the muscle fibres showing a tendency to fall apart). The acute and widespread nature of the myocarditis was confirmed later on microscopical examination of prepared sections. On the surface was a considerable thickening of the epicardium (" milk spots "), covering the greater part of the posterior aspect of the right ventricle, the whole of the right auricle, and on the left ventricle chiefly following the course of the vessels. The right auricle and both the ventricles were markedly dilated, but the capacity of the left auricle was only slightly increased ; both the right auricle and the right ventricle showed considerable hypertrophy and the left ventricle a moderate amount.

The coronary arteries, pulmonary artery and valves appeared normal.

The tricuspid valve was healthy but the orifice slightly dilated.

The mitral orifice was dilated, admitting three fingers, while the valves were free and normal, excepting at the extreme base of the anterior cusp, the appearance of which is described below.

The aortic valve showed ulcerative endocarditis affecting the left posterior cusp, the other cusps appearing normal. The basal portion only of the left half of the left posterior cusp was involved ; the free edge was quite unaffected, but below this, between the edge and the base, there was a large perforation more or less circular in shape and about ⅜ inch in diameter. The lower edge of the opening reached the base of the cusp ; the margins were ulcerated, and projecting from it into the ventricle there was a massive fibrinous and fairly tough vegetation. The latter structure was about a quarter of an inch thick and projected a distance of half an inch from the cusp. Microscopic sections prepared from this vegetation, including the piece of aortic cusp to which it was attached, showed large numbers of cocci exhibiting the morphological appearance and staining reactions of the meningococcus. Other vegetations apparent at the edge of the perforation encroached to a slight extent on the base of the anterior mitral cusp, where it and the aortic cusp meet.

Aorta.—A small circular aneurism, $\frac{1}{4}$ inch in diameter, was seen immediately above the perforation in the cusp ; it penetrated the inner and middle layers of the aorta, its base being formed by the external coat. A few fatty streaks were found in the tunica intima, but no atheroma or evidence of syphilis.

Lungs.—The right lung showed old pleural adhesions of the outer and posterior surfaces of the upper lobe, and also of the posterior surface of the lower lobe in its upper portion. There were no adhesions on the left side nor to the diaphragm. A certain amount of chronic bronchitis and emphysema was also apparent.

Liver. — Much enlarged, the weight being $90\frac{1}{2}$ oz. There was nothing abnormal visible to the naked eye.

Spleen.—Also enlarged (weight 18 oz.) ; it showed old adhesions, the pulp was soft and friable and a few recent infarcts were present.

Kidneys.—Both enlarged generally but no other apparent change.

R. L. Cecil and W. B. Soper in 1911 reported a case of meningococcal endocarditis in association with arthropathies, proved by blood culture and autopsy, which terminated fatally on the tenth day of observation without developing meningitis. The patient, aged 31 years, during the two weeks preceding his admission to hospital had complained of sore throat, feverishness, pain and tenderness in the right wrist and elbow, headache, and finally vomiting. On admission, he exhibited acute swelling and tenderness of some of both the larger and smaller joints, and a presystolic murmur at the cardiac apex ; there were no signs of meningitis. In view of the clinical evidence, a diagnosis of acute rheumatism with endocarditis was made. During the next few days pyrexia increased and the patient became delirious ; blood culture yielded the meningococcus. On the ninth day, a few petechial spots appeared over the trunk, and death occurred on the following day. Autopsy revealed ulcerative endocarditis with infarcts in the spleen and kidneys ; no meningitis was present.

Arthritis.—The occurrence of a swollen joint unassociated with meningitis, and which on culture of the fluid obtained by aspiration yields meningococci, has occasionally been noted. For example, the following instance is recorded by Flack :

Private P. returned from France on leave on July 18. On July 27, one of his children was taken ill with cerebro-spinal fever and died on the following day. A naso-pharyngeal swab taken from Private P. yielded many colonies of Type IV. (Gordon) meningococcus. His other three children were subsequently removed to an isolation hospital. One child was suffering from pyrexia (temperature 101° F.), and on

lumbar puncture the cerebro-spinal fluid was found clear and showed no cocci or increased cell content. From the fluid of a swollen knee-joint, however, a Type IV. (Gordon) meningococcus was cultivated. A blood culture taken one day after the appearance of the joint lesion proved sterile.

Reference has already been made to cases in which septicaemia with arthropathies precedes meningitis (Chapter VIII. p. 196). In Soloman's case, the septicaemia and arthropathies persisted for two months before the patient developed meningitis ; in the example mentioned by Sophian, the joint lesions were present for three weeks before the supervention of meningitis.

Conjunctivitis.—T. C. Ker and R. O. Douglas, in Australia, reported the case of a nurse, on duty in the cerebro-spinal fever isolation block, who developed a right-sided conjunctivitis with a profuse purulent discharge. Smears from the lower fornix of the conjunctiva showed pus cells with many Gram-negative diplococci both intracellular and extracellular. These authors state that " the cultures gave a rapid profuse growth of apparently typical meningo-coccal colonies in all three tubes inoculated ; in two cases the growth was in pure culture, so far as could be told by examination of the colonies and by staining them." No meningitis or generalised infection occurred. Three days after the initial symptoms of con-junctivitis the left eye also became affected, the discharge being profuse but not reaching such a severe degree of inflammation as that of the right eye. Four days later the left eye had quite recovered and the right almost so. Meningococcal conjunctivitis was observed in several of the cases of cerebro-spinal fever, but in no case was it of such a fulminating character as in this case in which no generalised infection occurred.

CHAPTER XV

IN order to describe the pathological changes that occur in cerebro-spinal fever it is necessary briefly to recall the relationship of the brain and spinal cord to their surrounding membranes.

The Meninges.—The membranes constituting the immediate coverings of the central nervous system are three in number—the pia mater, arachnoid mater and dura mater.

The pia mater is a delicate fibrous membrane containing numerous small blood vessels, and follows closely the irregularities of the brain and spinal cord ; it penetrates into the sulci and projects into the cerebral ventricles carrying with it a network of capillaries known as the choroid plexus. This network is covered by a layer of epithelium which plays an important part in the secretion of the cerebro-spinal fluid (*vide* Chapter X. p. 232). The pia mater, therefore, forms the innermost layer of the meninges. The spinal pia mater is thicker and denser than the cerebral and more adherent to the subjacent nervous tissue.

The arachnoid mater is a delicate non-vascular membrane investing loosely the brain and spinal cord, and placed externally to the pia mater. Between the arachnoid and pia mater there is a space—the subarachnoid space—in which circulates the cerebro-spinal fluid. Delicate septa and numerous trabeculae (sub-arachnoid) traverse this space and connect the arachnoid to the pia mater. At one part of the brain only are the arachnoid and pia mater at all firmly adherent ; this occurs in the region of the Pacchionian bodies, which consist of invaginations of the arachnoid through the dura mater into the superior longitudinal sinus. Over the gyri of the cerebral cortex the subarachnoid space is merely potential, but as the arachnoid bridges across the sulci and does

not dip into them, distinct intervals are formed in these situations, which, since the larger vessels run in the sulci, constitute considerable perivascular spaces. At the base and lateral aspects of the brain there occurs a much wider separation between the arachnoid and pia mater ; the portions of the subarachnoid space thus formed are known as " cisternae." Of these the most important are the cisterna basalis, the cisterna pontis, and the cisterna magna or cerebello - medullaris. The cisterna basalis, extending anteroposteriorly from the pons Varolii to in front of the optic chiasma and laterally between the two projecting temporal lobes, encloses the interpeduncular space and circle of Willis. The cisterna pontis is formed as the arachnoid stretches across the interval between the posterior part of the pons and the medulla oblongata ; it contains the basilar artery and is continuous with the anterior portion of the subarachnoid space of the spinal cord. The cisterna magna is situated between the cerebellum and the medulla, being enclosed by the reflection of the arachnoid from the back part of the under surface of the cerebellum on to the roof of the fourth ventricle. This, the largest and most conspicuous of the cisternae, communicates freely with the cavity of the fourth ventricle by means of the median foramen of Magendie and the lateral foramina of Luschka; these have already been mentioned when dealing with hydrocephalus (Chapter IX. p. 219).

In the spinal canal the subarachnoid space is considerably larger and more capacious than that surrounding the brain, the arachnoid and pia mater in most parts being separated by a fairly wide interval. The spinal cord itself lies suspended in this space, which contains a quantity of cerebro-spinal fluid and is traversed by the slender subarachnoid trabeculae which connect the arachnoid to the pia. The spinal subarachnoid space is also partially subdivided into anterior and posterior portions by the ligamentum denticulatum. This is a fibrous band attached longitudinally to the pia mater on either side of the spinal cord and extending outwards to the dura mater ; its outer margin is serrated, the denticulations pushing the arachnoid before them and becoming attached to the dura mater. It is by means of this structure that the cord is maintained in position. Further details concerning the spinal subarachnoid space are considered in connection with the operation of lumbar puncture (Chapter XVIII. p. 406).

The dura mater is a dense and thick fibrous membrane possessing a considerable degree of strength. It is the outermost layer of

the meninges and is separated from the underlying arachnoid by the subdural space, which in most parts of the central nervous system is merely a capillary interval. The cranial dura mater is composed of two layers intimately connected with each other but separating along certain lines to form channels lined with endothelium ; these channels constitute the venous blood sinuses.

In the spinal canal the dura mater forms a tube which encloses the spinal cord and extends from the foramen magnum above to the second or third sacral segment below, where it blends with the filum terminale externum.

Within the cranial cavity the dura mater is closely adherent to the bones of the skull and forms an internal periosteum. As it proceeds into the spinal canal, however, its two constituent layers separate. The inner layer is carried downwards as the cylindrical tube which encloses the spinal cord while the outer layer is prolonged downwards in connection with the periosteum and ligaments on the anterior wall of the vertebral canal.

Histological Changes in the Central Nervous System.—*Acute Stage.*—During the acute stage of cerebro-spinal fever the essential pathological process is a purulent inflammation of the arachnoid and pia mater. According to Westenhoffer, the primary lesion is localised in the arachnoid, that is, the disease consists of a suppurative arachnitis. This observer bases his assumption chiefly on the fact that in the depths of the sulci where the pia mater alone is present the inflammatory changes are much less marked than in the superficial portions and in some early cases are entirely absent. The earliest lesions, consisting of an intense polymorphonuclear infiltration, are seen in the vicinity of the blood vessels, which are markedly dilated ; most authorities agree with Busse that the changes are synchronous in the brain and spinal cord. Gradually the leucocyte infiltration of the meninges becomes more general, the fine trabeculae and septa connecting the arachnoid to the pia disappear, and spaces are formed containing masses of inflammatory cells. In many regions the subarachnoid space is filled with cells, chiefly polymorphonuclears, some of which exhibit disintegration. Between the cells is seen a finely granular material representing the coagulated serum of the exudate ; in the earlier stages there is very little fibrin. Four varieties of cells are usually present, the predominating one being the polymorphonuclear. Other cells, varying in size from twice to eight times that of the ordinary polymorphonuclear, show a faintly stained granular cytoplasm and a

large eccentric vesicular nucleus ; also they often contain a number of smaller ingested cells lying in vacuoles in the protoplasm. These cells were first described in 1865 by Boehmer, who considered them to be the parent cells of those cells seen inside them. Councilman, Mallory and Wright have been able to follow the steps of the formation of these large cells from the connective tissue cells of the meninges ; they may also arise from the adventitia of the smaller blood vessels. Some observers have demonstrated their existence in forms of meningitis other than meningococcal. Of other cells, lymphocytes and red blood corpuscles are present in variable numbers. It has been said that eosinophiles are almost always absent, but Foster and Gaskell found them fairly frequent in small numbers.

In the exudate, meningococci are usually present in quantity, both intracellular and extracellular. In the meninges themselves, especially those of the spinal cord, the organisms are less abundant; they may be found, however, in the walls of the perivascular spaces of the subarachnoid cavity. According to Foster and Gaskell, meningococci are difficult to find inside the polymorphonuclear leucocytes in sections of the meninges, and it is possible that they are only ingested to an appreciable extent after becoming free in the subarachnoid space. In support of their view, these observers mention the fact that extracellular cocci are more numerous in the last portions of cerebro-spinal fluid withdrawn by lumbar puncture ; this fluid, presumably from the region of the cerebral meninges, contains the cocci which have freshly escaped from the walls of the perivascular spaces and have not yet become ingested by leucocytes.

The changes in the meninges of the spinal cord are similar to those described above excepting, however, that the large cells are not so numerous.

The ventricular walls and neighbouring brain tissue also show marked changes. In places the ependymal lining may be completely lost and the villi of the choroid plexus show some desquamation. The subependymal tissue becomes reticular and oedematous, while the neighbouring vessels are dilated and are surrounded by leucocytes either isolated or in groups. The villi of the choroid plexus are also congested and infiltrated with leucocytes.

The pathological changes may also affect the substance of the brain and spinal cord. The cerebral cortex is frequently found oedematous, and scattered leucocytes are often present in the

outermost zones of the cortex—in the tissue above the ganglion cells ; at times, leucocytes are also found in the white matter of the brain. The cortical blood vessels are dilated and in many cases show perivascular leucocytic infiltration. Councilman, Mallory and Wright describe proliferation of the neuroglia and connective tissue cells in the outermost part of the cortex, in the subependymal region of the ventricles, and in the vicinity of foci of haemorrhagic and cellular infiltration. Netter has described changes in the actual nerve cells, such as chromatolysis and vacuolisation ; in Foster and Gaskell's experience, however, these changes, if present, are extremely slight. Meningococci have been demonstrated in areas of focal softening affecting the brain substance.

In the spinal cord perivascular leucocytic infiltration may be of considerable intensity affecting chiefly the region of the posterior horns. In one of Foster and Gaskell's cases the infection was so acute that perivascular haemorrhages of considerable extent had occurred in the substance both of the brain and cord ; these were most intense in and around the posterior horns of the cord but were also found in the region of the anterior horns.

Chronic Stage.—With the progress of the inflammation, the greater number of cells in the exudate undergo degeneration and fatty metamorphosis ; the nuclei lose their staining power and become converted into granular debris. The large cells disappear while lymphocytes and plasma cells appear in large numbers. Organisation of the exudate takes place by the formation of new connective tissue and capillaries (Heiman and Feldstein).

In subacute and chronic cases the pyramidal cells and cells of Purkinje (in the cerebellum) show evidence of degeneration in the form of chromatolysis and vacuolisation. Along the outer border of the cerebellar cortex Busse has observed a continuous layer of cells with nuclei placed at right angles to the circumference of the cerebellum (palisade cells). They are normally seen in foetal life and early infancy, and Busse interprets their presence in the chronic stage of meningitis as a reversion to the foetal structure.

In the spinal cord, Liebermeister, Lebsanft and Netter have described destruction of the myelin sheaths and degeneration of the fibres of the peripheral zone. The process was more particularly marked in protracted cases. Some evidence of degeneration has also been seen in the cells of the anterior horn ; the cells of the spinal ganglia may show similar changes.

In chronic cases, as a result of the purulent infiltration of the

surrounding arachnoid, the posterior nerve-roots may exhibit degeneration.

The cranial nerves are often involved as a result of the extension of inflammation along the arachnoid which envelops them. The Gasserian ganglion is often found embedded in pus at an early stage of the disease.

Macroscopical Changes in the Central Nervous System.—The naked eye changes found on post-mortem examination vary considerably with the duration of the disease and clinical type of case. As a rule, however, on removing the skull cap the dura mater is found tense and its vessels show pronounced congestion. Its inner surface is shiny and small haemorrhages may be present in those portions covering the base of the brain. Some degree of flattening of the cerebral convolutions is present but it varies in amount with the type of case.

Fulminating Type.—There is a generally increased tension of the dura mater together with injection of the vessels on its internal surface. The blood vessels of the cerebral cortex as well as the smaller pial vessels, are intensely congested, at times giving a reddish tinge to the entire surface of the brain. The surface of the arachnoid is lustreless and occasionally adherent to the dura. In the sulci on the upper and lateral aspects of the cerebrum a small quantity of turbid fluid is usually seen, and not infrequently small patches of purulent exudate. Many authorities state that in fulminating cases no definite pus is present but this is by no means invariable. Foster and Gaskell, for instance, in six of nine fulminating cases found pus either at the base or convexity of the brain, or both.

In our experience, as pointed out in Chapter VII. (p. 138), two varieties of the fulminating type occur ; in the first variety the patient apparently succumbs to the overwhelming intensity of the blood infection, the meningitis being comparatively slight, while in the second death occurs rather from an intense infection of the cerebro-spinal system.

In the former case the meninges are found intensely congested and there is a slight excess of fluid, turbid in character, at the base of the brain, and possibly in the ventricles, together with a few small fibrinous flakes. In the second variety, in addition to the general congestion, some purulent exudate is present along the margins of the blood vessels as they proceed up the lateral aspects of the cerebrum as well as in the cisterna basalis and cisterna magna.

The whole brain may appear oedematous, and localised areas

of haemorrhage be present in the meninges. In one case dying within twelve hours of the onset, recent haemorrhage into the meninges was found over the lateral aspect of the left temporo-sphenoidal lobe ; the area was about two inches in diameter. A second smaller haemorrhagic area was also present in the upper part of the parietal region.

As a rule the ventricles show little or no distension but they may contain turbid fluid ; in one of our cases, however, the fourth ventricle was markedly distended with turbid fluid. Petechial haemorrhages in the ependyma may be found.

In some cases a small amount of purulent exudate also extends down the spinal cord, the theca of which usually contains excess of turbid fluid.

Acute Fatal Type.—In cases of this type considerably more purulent exudate is present. The pus is greenish-yellow in colour, thick and gelatinous, and is usually abundant at the base of the brain—in the interpeduncular space, over the pons, medulla and cerebellum—from which situation exudate is seen extending along the perivascular spaces over the lateral aspects of the cerebrum to the vertex.

The meninges are readily stripped off the brain tissue ; the brain itself usually appears soft, friable and oedematous, and often exhibits petechial haemorrhages throughout the white and grey matter. Local collections of pus may be present over the vertex, particularly in the neighbourhood of the median fissure. In some cases there is found a cap of purulent exudate covering the upper and lateral surface of the frontal lobes and anterior half of the parietal lobes. This peculiar localisation is attributed by Goeppert to the distribution of the anterior and middle cerebral arteries.

The dura mater spinalis is distended and contains excess of purulent fluid. The exudate is confined almost wholly to the posterior aspect of the cord, being most abundant in the cervical, lower dorsal and lumbar regions. There is considerable injection of the meningeal blood vessels in the anterior part of the cord.

The ventricles are usually somewhat dilated and contain excess of turbid fluid and small purulent flocculi ; in the descending horns of the lateral ventricles the fluid may be more purulent. There is never, however, any marked hydrocephalus. The ependymal lining is lustreless, often exhibiting petechial haemorrhages, and the choroid plexus is markedly hyperaemic.

Areas of softening in the brain and cord are rare. In one of our

cases, however, dying on the seventh day of illness, an area of softening was found extending upwards from the base, and encroaching upon the head of the caudate nucleus ; the area was about the size of a walnut.

Thrombosis of the cerebral sinuses may be found. In one case examined by us the posterior half of the longitudinal sinus was filled with purulent and disintegrating blood-clot.

Progressively Purulent Type.—The post-mortem appearance in these cases fully coincides with the clinical observation that on repeated daily lumbar puncture the fluid withdrawn gradually becomes increasingly more purulent until finally only a drop or two of thick pus escapes. The dura is usually tense and the cerebral convolutions flattened. The base of the brain is found thickly coated with dense purulent exudate, pus being plastered over the pons, medulla and cerebellum, and completely obscuring these structures from view. The vertex and lateral aspects of the cerebrum may exhibit little or no exudate, but not infrequently patches of pus are scattered here and there, usually in the neighbourhood of blood vessels or of the superior longitudinal sinus ; the quantity, however, is insignificant as compared with the large accumulation at the base. The ventricles are frequently distended with thick pus, the lateral and fourth ventricles being chiefly affected ; in one of our cases the whole of the ventricular system was dilated with dense exudate.

The changes around the spinal cord are similar, the structure being covered throughout its length with thick purulent exudate which usually completely fills the intrathecal sac. When repeated lumbar puncture has been carried out there is little or no free fluid present.

Subacute Types.—Subacute cases or those becoming subacute and dying for some reason (*e.g.* untreated) between the second and fourth week of illness, exhibit a somewhat similar distribution of basal exudate to that of the acute fatal type described above. The distribution of pus over the vertex, however, is not nearly so widespread and may be absent, and the general congestion is by no means so intense. Adhesions between the pia and the arachnoid or the dura and the arachnoid may be found. Small portions of the subarachnoid space containing turbid fluid may become shut off by such adhesions (so-called sacculated meningitis).

Chronic Types.—Cases proving fatal after six weeks of illness seldom show any definite exudate over the upper and lateral aspects

of the cerebrum. The convolutions are markedly flattened, there is little or no congestion and the exudate is replaced by local or general thickening of the meninges, yellowish-white bands often being seen adjacent to the blood vessels. At the base, adhesions between the meninges and the brain substance are frequent ; in some cases, even after a course of six weeks or more, fibrino-purulent exudate is found plastered over the pons and medulla and in the region of the cisterna magna. The adhesions and fibrino-purulent exudate in the region of the medulla and the cerebellum may lead to mechanical blockage of the foramina of Magendie and Luschka and the consequent development of internal hydrocephalus, the mechanism of which has already been described (Chapter IX.).

Owing to the development of a certain degree of internal hydrocephalus in all chronic cases the ventricles are found markedly dilated and contain excess of fluid ; in long-standing cases the fluid may be quite or almost clear, but usually fibrinous flakes and occasionally purulent exudate are found in the most dependent parts of the inferior and posterior horns of the lateral ventricles, the extremities of which are more dilated than the rest of the cavity. As a rule the fourth ventricle especially shows some distension, while the Sylvian aqueduct and foramina of Monro are also enlarged. The third ventricle tends to be dilated but owing to its anatomical relations the distension is chiefly towards its weak antero-inferior wall, the tuber and lamina cinerea are consequently stretched and bulge. The ependymal lining of the ventricles usually exhibits changes which, however, vary in different cases. According to Joslin, it may be either swollen and velvety, slightly or markedly granular ; in places it is often destroyed and replaced by granulations. The choroid plexuses are as a rule pale in appearance, but occasionally show hypertrophy and vesiculation.

The meninges of the spinal cord also show thickening and opacities, but these changes are almost always confined to the posterior aspects of the cord and are less marked than in the meninges of the brain ; scattered patches of fibrino-purulent exudate may occasionally be found. In some cases the thecal membranes become adherent to the cord and the adhesions may be sufficiently extensive as to lead to occlusion of the subarachnoid space ; the fluid exudate is consequently held up and hydrocephalus develops. False membranes are sometimes found about the spinal nerve-roots. The parenchyma of the brain and cord show practically no naked-eye changes.

The post-mortem appearances in the posterior basic type of infants differ little from those of adult chronic cases. Yellow fibrino-purulent exudate is usually found over the pons, medulla and cerebellum, spreading inwards towards the ventricles and down the posterior aspect of the cord. Langmead states that some inflammation about the vertex was found in 19 of 50 autopsies on cases of this type. The ventricles are almost invariably dilated with clear or turbid fluid, together with the usual findings of hydrocephalus ; as a result of internal tension the cerebral walls may be considerably thinner than normally.

Pathological Changes in other Organs.—*Gastro-intestinal Tract.* —In fulminating cases the mucous membrane of the stomach may exhibit numerous petechiae. In other acute cases marked injection of the blood vessels is present and occasionally haemorrhagic erosion ; Busse considers that this may be due to repeated vomiting.

In the intestinal mucosa petechial effusions may also be present, and a diffuse pinkish staining is not uncommon in acute cases. Denehy mentions one case in which the intestine was filled with blood-clot. Swelling of Peyer's patches and of the solitary follicles has been noted in many fatal cases. The constancy of these lesions originally led Goeppert and others to express the belief that the gastro-intestinal tract was the portal of entry of the meningococcus, an idea long since abandoned. The mesenteric glands are not infrequently enlarged. Symmers and Wilson regard this glandular enlargement to be due to a secondary invasion by certain intestinal bacteria, the meningococcal infection having produced a lowering of resistance to such organisms (*vide* Chapter XI. p. 301). Similar changes in the mesenteric glands and lymphatic follicles, however, are present in a number of other acute infections.

Heart.—Acute fibrinous or purulent pericarditis may be found in acute fatal cases ; as a rule the exudate is fibrino-purulent in character and is usually more marked on the anterior aspect of the heart than on the posterior. In our experience, meningococci are exceedingly difficult to demonstrate in films of the pus. Fulminating cases frequently exhibit subpericardial haemorrhages.

In acute cases the cavities of the heart usually show some general dilatation, those on the right side being slightly more affected than those on the left. The organ in such cases is flabby, of increased friability and exhibits cloudy swelling. Occasionally the myocardium may show degenerative lesions. Westenhoffer

describes diffuse and circumscribed infiltration of the musculature and also fatty degeneration of the actual fibres.

As a complication, endocarditis is occasionally seen ; in such cases meningococci have been demonstrated in the vegetations by Weichselbaum and Ghon and Westenhoffer. In rare cases a meningococcal endocarditis occurs without meningitis. Such a case coming under our observation is fully described on p. 347 (Case LIX.), together with the post-mortem appearances ; meningococci were present in sections of the vegetations from the valves.

Blood Vessels.—Staining of the lining membranes of the arteries is rare even in fulminating cases. Septic thrombosis is occasionally found in the cerebral sinuses ; in one of our cases the posterior half of the superior longitudinal sinus was filled with purulent and disintegrating clot.

Respiratory Tract.—Evidence of inflammation of the bronchial mucous membrane is not infrequent in acute cases. Purulent bronchitis is occasionally present. In fulminating and acute cases passive congestion of the lungs, atelectasis, foci of broncho-pneumonia and interstitial emphysema may be found.

Subpleural haemorrhages are frequent in the fulminating type, and in other cases pleurisy with serous, sanguineous or purulent effusion has been met with in somewhat rare instances. Terminal hypostatic congestion is present in about 30-40 per cent of cases coming to autopsy.

Pharyngitis, sphenoiditis and ethmoiditis have already been mentioned in previous chapters.

Liver.—In acute cases the liver usually shows congestion or cloudy swelling ; other changes are very rare. The occurrence of a yellowish liver with areas of degeneration has been described by Symmers and Wilson.

Spleen.—Changes in the spleen are somewhat variable in appearance. Some authors state that as a rule there is no enlargement of the organ even in fulminating and acute fatal cases. On the other hand, Dènehy in 70 autopsies found that the spleen showed appreciable enlargement in 29 (41 per cent). In our experience fulminating cases generally exhibit at least some degree of enlargement, the pulp being soft and the organ friable. One fulminating case coming under our observation showed a spleen almost twice the normal size. In acute fatal cases the spleen may or may not be enlarged ; the pulp is often soft and congested and, more rarely, a few haemorrhagic patches are found. In other cases the organ

does not usually exhibit any definite changes. When endocarditis is present as a complication the spleen may be the site of infarction.

Kidneys.—The kidneys show no very constant changes. The most frequent lesion, however, is cloudy swelling, and according to Heiman and Feldstein, fatty degeneration of the lining of the tubules is not uncommon. Reference has already been made to nephritis occurring as a complication (Chapter VIII. p. 192).

Adrenal Glands.—In fulminating cases haemorrhage into the substance of the adrenal bodies is not infrequently found. The glands appear dark red in colour and weigh from 24 to 28 grms. Microscopically the medullary substance is replaced by effused blood and very few chromaffin cells are visible. The capillaries of the cortex are distended, haemorrhagic effusion is seen between the cells, and the number of refractile granules is much diminished.

Bladder, etc.—Owing to prolonged retention or overflow incontinence of urine, cystitis may be present in subacute and chronic cases. In acute cases congestion of the mucous membrane of the bladder is sometimes seen and occasionally petechial haemorrhages. Purulent cystitis with sloughing of the mucous membrane has been described.

Inflammatory changes in the urethra or seminal vesicles are rare ; Pick, however, records a case in which double empyema of the seminal vesicles occurred, meningococci being readily demonstrated in the exudate.

CHAPTER XVI

WITH a disease so variable in its course as cerebro-spinal fever, prognosis is often extremely difficult to determine. Cases admitted to hospital in an apparently hopeless condition of coma may recover, while others, from all appearances mild in character, prove fatal owing to the subsequent development of hydrocephalus or of a progressive increase in the purulency of the cerebro-spinal fluid.

The various factors on which an opinion may be based, however, with special reference gained from our own series of cases, are as follows.

General Considerations.—*Early Diagnosis.*—This factor is of paramount importance as the earlier the disease is diagnosed the earlier is treatment instituted. All observers agree that early treatment is one of the most hopeful of prognostic indications ; our own cases, as shown in the section dealing with treatment (Chapter XVIII. p. 403), illustrates this well, especially in the more acute cases. Lumbar puncture should always be performed in doubtful cases rather than allow the opportunity for the early institution of treatment to pass; we have seldom indeed observed this small operation to have any bad effect on patients suffering from other diseases.

Stage of Epidemic.—Cases occurring late in an epidemic are usually milder and less fatal than the earlier ones. During the early stages of an outbreak fulminating cases are relatively more frequent.

Age of Patient.—The mortality is distinctly heavier among infants and adults over 40. Infants under 2 years of age show the greatest mortality, being over 80 per cent ; after 2 years, the death rate tends to decrease towards the 15th year. The mortality then rises, again showing a slight fall between 20 and 30. After 30 it rises considerably and increases with each subsequent decade.

The following percentages from cases admitted to the Mount Sinai Hospital, New York (1901–1906), are given by Heiman and Feldstein :

Age.	Mortality.
1 year	74 per cent
2 years	88 ,,
3-5 ,,	41 ,,
5-10 ,,	40 ,,
10-15 ,,	39 ,,
15-20 ,,	48 ,,
20-30 ,,	45 ,,
30-40 ,,	63 ,,
40-50 ,,	67 ,,
50-60 ,,	100 ,,

Other authors give lower mortality percentages but with practically the same comparative value.

In a series of military cases (1916–1917), of which we have the larger amount of data, the mortality in relation to age was as follows :

Age.	No. of Cases.	Mortality.
15-19 years	24	33 per cent
20-24 ,,	19	26·3 ,,
25-29 ,,	18	50 ,,
30-34 ,,	4	25 ,,
35 and over	5	40 ,,

2 patients aged 40 and 60 both died.

In serum-treated cases, the heavier mortality is still seen within the first two years of life. At this age, as pointed out previously, there is a tendency towards the more rapid development of hydrocephalus. The following table illustrates the mortality in relation to age in serum-treated cases :

Author=	Flexner.			Netter.			Dopter.		
Years.	No. of Cases.	Deaths.	Mortality per cent.	No. of Cases.	Deaths.	Mortality per cent.	No. of Cases.	Deaths.	Mortality per cent.
Under 1	129	64	49·6	18	15	61	.	.	48·6
1-2	87	27	31	15	4	26·6	.	.	20·1
2-5	194	55	28·4	22	6	27·2	.	.	9·3
5-10	218	33	15·1	21	2	9·5	.	.	8·5
10-20	360	106	4·4	11	2	18·1	.	.	10·2
Over 20	288	108	37·5	13	3	23	.	.	14·1

Previous Health.—The presence of chronic nephritis, chronic alcoholism or of latent tuberculosis seriously impairs a patient's chance of recovery. Apart from such conditions, general health and constitution have little apparent influence, as strong and robust individuals often die rapidly while those of poor physique recover.

Mode of Onset.—A gradual onset appears to be more favourable than one that is sudden and abrupt. Of 20 patients exhibiting the former type of onset, 3 only died (15 per cent), while of 50 in whom the disease appeared abruptly, 22 proved fatal (44 per cent). The fact that a short period of malaise preceded the sudden onset was of no prognostic value ; 22 patients fell into this category, 14 of whom recovered and 8 died.

The absence of vomiting at the onset, with the exception of fulminating cases, is of somewhat favourable import. Of 56 non-fulminating cases, 6 only did not vomit at the onset of the disease and all recovered. Early loss of consciousness does not necessarily indicate that the outlook is bad.

Type of Case.—Fulminating cases, of course, are invariably fatal. The prognosis in the posterior basic type is also very bad, the mortality being over 75 per cent. In subacute cases the outlook is more hopeful than in acute ; for instance, among our subacute cases the mortality was only 14 per cent as compared with 55 per cent in acute cases of all types.

Temperature, Pulse, etc.—In our experience, the temperature and pulse rate during the first day or two are guides merely to the severity of the disease and of no definite prognostic value. Continued hyperpyrexia during the course is of exceedingly grave import.

The appearance of extreme dyspnoea always foreshadows a fatal issue ; cyanosis also is an unfavourable sign.

Cerebro-spinal Fluid at the First Lumbar Puncture.—A purulent (yellowish) fluid obtained at the first lumbar puncture is a sign of graver prognosis than a merely turbid (whitish) one, but it is by no means indicative that the patient will not recover. Of our patients yielding a definitely purulent cerebro-spinal fluid at the first evacuation, nearly 50 per cent recovered. Excluding fulminating cases, among those showing merely a turbid fluid, recovery resulted in 77 per cent.

From the presence of numerous meningococci on microscopical examination in the first sample of cerebro-spinal fluid obtained no definite conclusions as regards prognosis can be drawn, but

failure to find the diplococci after prolonged search is distinctly favourable. Of seven patients in whose cerebro-spinal fluid no organisms could be seen, either on direct microscopical examination or in culture, only one died ; this case was of a progressively purulent type and meningococci were found on the following day. Of the other six, the organisms were subsequently obtained in three.

Type of Coccus.—In general, the isolation of a Type II. (Gordon) coccus appears to offer the most favourable prognosis, the mortality of our Type II. cases being 30 per cent as compared with 40 per cent for Type III. Type I. is somewhat resistant to treatment and usually gives rise to a severe form of the disease (mortality, 60 per cent).

Blood Pressure.—The presence of a continued low blood pressure, especially below 100 mm. Hg., during the first two days of illness is of grave significance ; Fairley and Stewart found that of 19 patients with an average blood pressure below 120 mm. during the first few days of illness, 17 died.

Subsequent to the early stages of the disease a continued average blood pressure of over 120 mm., especially if severe meningitis be present, is also an unfavourable sign ; the mortality among such cases is fully 70 per cent.

Special Features.—*Rash.*—A purpuric rash is an ominous sign. If well-marked vibices are present the case is nearly always fatal. Of nine cases showing well-marked purpuric blotches eight died ; four were of a fulminating type, three died within four days of the onset (acute fatal type), and the last case, after a severe course, terminated fatally on the 31st day of illness. The case that recovered (Case II. p. 63) was seen prior to the involvement of the meninges ; early treatment, therefore, may have been instrumental in avoiding a fatal issue. One other case, in whom only a few purpuric spots were seen on the legs in association with a general petechial rash, recovered about the 40th day of illness.

A petechial rash appearing on the first or second day is said to be an unfavourable sign. Of 17 cases, however, admitted on the first or second day of illness with well-marked petechiae, eight died and nine recovered.

The late appearance of a macular rash was considered a hopeful sign. Such a rash was observed in only 20 per cent of cases, the mortality among whom was under 30 per cent.

Mental Changes.—Intense restlessness, when it occurs early, is usually of rather more serious import than delirium or even

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unconsciousness. One patient was so restless and violent that he was admitted as a case of acute alcoholism; he died within four days. As delirium increases the worse becomes the prospect of a favourable termination. Hallucinations occurring after the third or fourth day are unfavourable; they were often present in the cases of the progressively purulent type, which invariably proves fatal. Cases in which mental symptoms are entirely absent almost always recover.

Condition of Sphincters.—From the presence of retention or incontinence of urine during the early stages of illness no conclusion as regards prognosis can be drawn. Retention or incontinence occurring late in the course is, however, an unfavourable development. In progressive purulent cases, which invariably prove fatal, retention is often late in appearance. When incontinence of urine is suddenly replaced by retention, the outlook is grave rather than otherwise; four patients in which this change was observed all died.

Head Retraction. — This symptom, occurring in adolescents and adults, is by no means the unfavourable sign that has been supposed by some writers. Of 23 patients, 18 years of age and over, who showed marked occipital retraction during the course, 14 recovered.

Herpes.—The presence of herpes has been thought to furnish a sign indicating that the chances of the patient's recovery are distinctly favourable. Although the majority of cases showing herpes recover, it is of no constant value in this respect. Among the patients of our series in which the symptom was present, the mortality was 23 per cent.

Motor Disturbances.—Catching at imaginary objects and picking at the bed-clothes (carphology and floccitation) are unfavourable signs. Also, a convulsive seizure occurring in an adult must be viewed with seriousness; in infants the convulsions have not the same significance. Nystagmus is often associated with internal hydrocephalus and consequently is of grave prognosis.

Abdominal Reflexes.—These reflexes are often diminished or absent early in the disease. Their increase or return is a sign that the patient is progressing favourably; similarly their disappearance is an unfavourable indication. Cases in which they are retained throughout usually recover.

Of 44 cases in which the condition of the abdominal reflexes were investigated daily, the following results were obtained:

In 21, present throughout the course. All recovered. (In 18 of these cases they were considerably reduced on admission to hospital, but increased as general improvement progressed.)

In 6, proving fatal, they were present on admission but disappeared as the patient became worse.

In 4, no reflex was obtainable on admission; their return was followed by improvement and ultimate recovery.

In 5, they were present at first, but disappeared with increased severity of the disease; with improvement the reflexes returned.

In 2, they were absent on admission but reappeared during a period of temporary improvement; they again disappeared, however, as the patient became worse.

In 5, fatal cases, they were absent throughout.

Arthropathies are considered by some authors to be of good prognosis as regards ultimate recovery from meningitis. In our experience the chances are about equal, the mortality being nearly 50 per cent in cases developing arthropathies.

Pneumonia.—The development of pneumonia as a complication is most serious but not necessarily fatal.

Pericarditis is almost always followed by a fatal termination. It occurs chiefly in cases of the acute fatal type and is rarely diagnosed during life.

The Occurrence of Hydrocephalic Symptoms must be viewed with extreme gravity. Repeated lumbar puncture, however, may alleviate the condition. Even when internal hydrocephalus appears to be present the prognosis is not necessarily hopeless. Six cases of our series showed symptoms indicative of marked hydrocephalus and eventually recovered, in one (Case XLVI. p. 227) signs of internal hydrocephalus, including " dry taps," were present.

Persistent Vomiting, unrelieved by lumbar puncture, is an ominous sign, and is usually associated with hydrocephalus.

The prognosis as regards recovery from complications such as paralyses, deafness, etc., was considered when each complication was dealt with (p. 199), and also in the section on Sequelae (Chapter XIX.).

The Cerebro-spinal Fluid during the Course.—*Quantity.*—The daily evacuation of 40-70 c.c. of cerebro-spinal fluid is more hopeful than when only small amounts are obtained; the latter may indicate impending hydrocephalus or increased purulency. A " dry tap," provided one is quite certain that the subarachnoid space has been entered, is a most unfavourable sign. At least three

different interspaces should be entered before a " dry tap " is conclusive.

Appearance.—Rapid or gradual decrease in the turbidity of the fluid is the rule as recovery proceeds, and is an indication that the case is progressing favourably, provided fair quantities are obtained.

Increase in the thickness and purulency of the fluid, leading to difficulty of withdrawal through the lumbar puncture needle, is one of the gravest of signs.   It is seen in cases of the progressively purulent type and invariably leads to a fatal result.

Glucose Reaction.—Persistent absence of glucose on testing the cerebro-spinal fluid with Fehling's solution is of distinctly bad prognosis.   Authors have differed considerably as regards the converse proposition.   Certainly in our series of cases, the return of glucose, having been previously absent, has in all cases heralded improvement.   A recrudescence, however, may occur, during which it again disappears.   Glucose invariably returns in the cerebro-spinal fluid as the patient recovers.

Permanganate Reaction (Global).—As stated when dealing with Boveri's reaction in relation to the cerebro-spinal fluid, a progressive decrease on the one hand, or increase on the other, in the period occupied by the time reaction may be respectively of good or bad significance.

Bacteriological Findings.—On the whole, failure to obtain the meningococcus on *culture* from fluids subsequent to that withdrawn at the first lumbar puncture is a good prognostic sign.   In recrudescent cases and in those running a long and severe course, a culture may be obtained at a late stage of the disease, although the case eventually recovers.

As regards direct microscopical examination of films of the cerebro-spinal fluid, the presence of intracellular organisms is generally a more favourable sign than when they are chiefly extracellular.   If extracellular forms predominate, the case is usually not doing well.

General Hygienic Measures.—The necessity for free ventilation with an ample cubic space of fresh air for each individual is a well-recognised principle in the prophylaxis of all disease. In the prevention of cerebro-spinal fever, the avoidance of people congregating in close proximity to one another in a confined space is of particular importance, especially when an epidemic is prevalent. By the neglect of this factor individuals susceptible to the disease are brought into contact with carriers of the meningococcus ; the latter, also, are enabled to communicate the organism to other individuals who, although not actually developing the disease, may in turn become carriers. Since the meningococcus soon perishes when exposed to temperatures lower than 22° C. (71·6° F.), air-borne infection can only take place in a very warm atmosphere. The tendency for individuals during the colder weather to collect in overheated rooms with the windows closed and natural ventilation shut off certainly provides conditions under which such infection might occur. Consequently, in barracks and billets the windows should be open day and night ; to prevent the necessity for closing them during windy or wet weather, Halliday Sutherland suggests a " weather board," 18 inches in depth, fixed inside the lower part of the window at an angle of 45°, the lower sash being screwed up one foot from the bottom. This author states that no further cases of cerebro-spinal fever occurred in a certain barracks when this measure was adopted, and the incidence of respiratory disease also showed a remarkable fall. The men, of course, should be supplied with bed-clothing of sufficient warmth.

The Procedure to be adopted on the Occurrence of a Case of Cerebro-spinal Fever.—The patient should at once be removed to

an isolation hospital or special ward ; failing this, the case is isolated in a separate room or, preferably, a whole floor is given up to the patient and his attendants. The prophylactic measures to be adopted with regard to preventing the spread of infection from actual cases of the disease is dealt with under the heading of Personal Prophylaxis.

As far as possible the " contacts " of the case should be segregated and swabs taken from the naso-pharynx of each to ascertain the presence or otherwise of the meningococcus. By the term " contacts " is meant those individuals living in the same house, taking meals or working in the same room as the patient at the time of and during the week preceding his developing the disease. In civil practice, apart from institutions, it is usually impracticable to segregate all the contacts of a case and keep them isolated until the results of the post-nasal swabs are known ; consequently, one has usually to be content merely with swabbing the naso-pharynx of each of the contacts and awaiting the result. Children, however, should certainly be kept from attending school until definitely negative. A period of quarantine as a preventive measure is in itself quite useless, since some carriers are known to harbour the meningococcus for as long a period as three months ; effectual control can only be guaranteed by the production of bacteriological proof that the naso-pharynx of contacts is quite free from the organism. The swabbing of contacts is done either at the nearest bacteriological laboratory or in the homes of the individuals concerned ; in the latter case the culture plates are taken to the dwelling, the sowing being carried out at the time the swab is taken. This proceeding, as shown by the figures of Bruns and Hohn, renders the result much more certain ; the despatch of swabs by post is practically useless. Although it is doubtful if Bruns and Hohn differentiated the meningococcus with sufficient accuracy from other Gram-negative organisms, their results nevertheless show a progressive diminution in the number of positive results obtained, according to the length of time elapsing between the taking of the post-nasal swab and the sowing on the culture plate. Thus—

Swabs sown immediately on being taken = 32 per cent positive.
   ,,   brought by special messenger   = 17   ,,   ,,
   ,,   sent by post within 24 hours   = 4·7   ,,   ,,
   ,,   sent by post within 48 hours   = all negative.

The fact that the percentage of positive results is somewhat

high renders it doubtful that Bruns and Hohn were dealing solely with the meningococcus. This, however, in no way affects the record as an illustration that the longer the period that elapses between the swabbing and the sowing on the plate, the less likely are Gram-negative cocci resembling and including the meningo-coccus to be cultivated. It is further advisable, even though the swab be sown immediately after taking, to keep the plates warm, at about a temperature of 37° C., during the journey back to the laboratory, in order to ensure that the organisms do not perish in transit. This may be done by placing them between indiarubber hot-water bottles or by means of a special plate carrier consisting of a copper cylinder with double walls, enclosing a space which communicates with the exterior by means of a small opening fitted with a screw-cap. Hot water is poured into the cylinder through this opening. A copper skeleton frame, of suitable diameter for carrying the plates, fits into the interior of the cylinder, a lid being placed over the top. Such a plate carrier can be sterilised at frequent intervals, and in our experience is most satisfactory.

The bacteriological discovery of carriers, with their appropriate treatment, is one of the most important measures in checking the epidemic spread of the disease. When definite carriers are identified they are kept in isolation and treated by one or other of the measures described later, until the naso-pharynx is free from meningococci, as indicated by not less than two successive swabs, taken at an interval of several days, yielding a negative result.

Although the vitality of the meningococcus apart from the body is slight, it is as well, as a precautionary measure, to disinfect the patient's dwelling, etc., by the usual recognised methods (e.g. formalin spray). Linen, etc., is usually removed by the sanitary authorities for disinfection.

By the means described above, if systematically carried out, experience has shown that even in large cities efficient control over the spread of the disease can be adequately maintained.

As regards the prevention of military outbreaks of the disease, the following are the measures adopted in the British Army upon the recommendation of Surgeon-Colonel R. J. Reece:

On the patient's removal to an isolation hospital or ward, dis-infection of all his clothing, bedding, feeding utensils and quarters is carried out. All contacts are then segregated and afforded ample space in freely ventilated quarters. At the earliest possible moment a bacteriological examination of the naso-pharynx of

each contact is made. While awaiting the result, it is recommended that the isolated men, if physically fit, be drilled daily in the open air. Those in whom the swab proves negative are returned to duty, provided the throat is normal. Carriers are transferred to isolated quarters in hospital and treated until two successive swabs, taken from the naso-pharynx at several days' interval, are reported as negative.

Further recommendations are as follows : that special attention be directed towards cases of sore throat, headaches, etc., suggesting influenza ; barrack-rooms, mess-rooms, canteens, billets, etc., occupied by the unit in which the case occurred, be examined to rectify any overcrowding and to secure ample ventilation ; should three, four, or more cases of the disease occur within a few days of one another in the same station, a representative sample (*e.g.* 50-100) of those men who have not been in contact with a case be examined bacteriologically. If this examination proves that a high percentage (*e.g.* 20 per cent) of carriers exists among the general military population, an attempt should be made to reduce the number of carriers by causing as many men as possible to pass through an inhaling chamber, the air of which is kept charged with a suitable disinfectant by means of a steam atomiser (*vide* Treatment of Carriers, p. 383). It is advisable to continue this treatment until it is found that no further reduction in the local carrier rate occurs. When the camp or depot is one into which recruits are received on joining, all recruits may also be examined on arrival to ascertain the " carrier rate " among them. If this examination tends to show that infection is being introduced by recruits, they should be treated for a week by means of the steam atomiser.

The use of an inhaling chamber together with bacteriological control might be usefully applied in the case of schools in any district where cerebro-spinal fever has broken out among children, and is threatening to assume epidemic proportions.

Personal Prophylaxis.—Any discharges escaping from the nose and throat of the patient, from the conjunctivae or from herpetic eruptions, as well as the excreta, should be carefully disinfected ; it is also necessary, as a precautionary measure, to sterilise all feeding utensils, bed linen, etc., in spite of the fact that the vitality of the meningococcus apart from the body is feeble. Cerebrospinal fluid must be handled with particular care. Attendants upon patients suffering from cerebro-spinal fever should always

wear overalls ; some writers consider that masks covering the nose and mouth are also advisable. Nurses, orderlies, etc., should be directed to use from time to time a mild antiseptic nasal douche. About once in three weeks, and especially if going on leave, all attendants should be " swabbed " in order to ensure that the meningococcus is not present in the naso-pharynx. Visits by the patient's relatives should be strictly limited in number and duration ; the visitor must wear an overall and cotton mask and must be allowed only to approach within a certain distance (2-3 yards) of the bedside of the patient. In addition, it has been our custom to take a post-nasal swab from the relative at the termination of a series of several visits.

TREATMENT OF CARRIERS

General Treatment.—Carriers must be isolated in quarters in which there is an abundance of fresh air ; on no account must they be housed together in intimate contact for, although infrequent, cross infection is known to occur. With regard to military cases, we have often placed carriers in tents, not more than one man being allowed in each tent. They should also be kept in the open air as much as possible during the day ; under such conditions many carriers tend to rid themselves of the meningococcus in a few days. Most authorities are agreed that whatever the form of treatment, a spell of sunshine and dry weather exerts considerable influence upon the disappearance of the organism from the naso-pharynx. Flack noted that in the dull weather of February and March 1916 the rate of discharge of carriers from isolation was very slow, whereas with the appearance of fine weather at the beginning of April the rate of discharge was rapid ; further, during this spell of fine weather, carriers who had been in isolation during most of February and March also became free. In some measure, this may be accounted for by the fact, as proved experimentally by Leonard Hill, that the circulation and secretion of the nasal mucosa is definitely influenced by weather conditions.

In general, the duration of the period of " carrying " varies according to the degree with which the carrier is infected ; those whose naso-pharyngeal swabs yield only a few colonies of meningococci usually become free more rapidly than those who yield a pure and copious growth. Also, there is no doubt that nasal

deformities and chronic inflammatory conditions of the naso-pharynx or accessory sinuses of the nose—deflected septum, chronic rhinitis and pharyngitis, adenoids and antral or ethmoidal disease —conduce to the prolonged harbouring of the meningococcus, carriers in whom such conditions exist being extremely difficult to render free from the organism. These abnormalities, if present, should receive appropriate treatment.

Convalescent Cases of Cerebro-spinal Fever.—Care must be taken to ensure that all patients recovering from the disease are free from the meningococcus on leaving hospital. The number of cases, taken all the year round, which continue to harbour the meningococcus during convalescence is, in our experience, about 30 per cent of cases recovering ; during the winter months the percentage is considerably higher, in our series nearly 50 per cent. It has always been our custom to obtain at least three negative swabs before allowing the patient to leave hospital.

Local Treatment. — Considerable difference of opinion exists among various authors as to the precise value or otherwise to be placed upon local treatment applied to the naso-pharynx. Many of the reporters to the Medical Research Committee during 1915 asserted that in their opinion local treatment was valueless ; in one report only, that of Gregor and Lindsay, was it contended that local treatment was of any great value. The meningococcus, however, being one of the least resistant to disinfectants of all pathogenic organisms, is rapidly killed by some of the mildest antiseptics in a concentration easily tolerated by the mucous membrane of the naso - pharynx. Theoretically, therefore, the organism should be destroyed in the naso-pharynx with comparative ease, provided it were reached by a suitable disinfectant. Strong antiseptics may be positively harmful, since, by injuring the delicate mucous membrane, they may set up inflammatory trouble and thereby render the meningococcus more difficult of elimination ; Tulloch, for instance, found that one per cent formalin actually retarded the disappearance of the organism.

Numerous antiseptics from time to time have been employed by different observers with widely varying results. Many have applied the disinfectant in the form of gargles and sprays ; it is obvious, however, that neither of these methods ensures the antiseptic reaching the naso-pharynx in its upper part—where the meningococcus is most frequently found—and consequently no definite result can be expected. A more efficacious method would

seem to consist in using the disinfectant solution as a nasal douche, the fluid being introduced via the nostrils and expelled through the mouth.

Among the methods that have been employed the following may be reviewed :

Kolle and Wassermann recommended nasal insufflation of dried anti-meningococcal serum. The results in eight cases thus treated by Kutscher were said to be satisfactory.

Pyocyanase, introduced by Escherich, is said to exhibit a solvent action on the meningococcus in vitro, and was used with apparent success by Jehle. It appears, however, that its solvent action is greatly reduced in the presence of an albuminous solution ; moreover, according to Haber, the action was lost when the naso-pharynx showed evidence of irritation.

Colebrook and Tanner tested the action of a number of substances upon the meningococcus in a film of nasal mucus. They found that the most effective antiseptic was a mixture of 2 per cent carbolic acid and a 5 per cent watery suspension of argentide. Persistent carriers were therefore sprayed several times daily with 3 per cent argentide ; the substance was found to be non-irritating and in many cases rendered the pharynx temporarily free from the meningococcus. In a few days, however, the organism reappeared, and in only one case was the treatment permanently successful. These observers concluded, therefore, that the naso-pharynx cannot satisfactorily be reached by sprays. Other substances tried include zinc sulphate and anti-meningococcal serum. An attempt was made to replace the meningococcus with the pneumococcus by the application of cultures of the latter organisms to the naso-pharynx. This, however, also proved unsuccessful.

Vincent and Bellot suggested the following inhalation :

Iodine	.	.	.	.	.	12 gms.
Guiacol	.	.	.	.	.	2 gms.
Thymol	.	.	.	.	.	35 centigms.
Alcohol (60 per cent)		.	.	.	200 gms.

Potassium iodide (gms. 6) is added to dissolve the iodine, and the mixture placed in a porcelain dish which is floated on a basin of boiling water. The patient sits with his head bent over this, at a distance of a few inches, and inhales the fumes, breathing slowly through each nostril for 2-3 minutes. This procedure is repeated five times in the 24 hours.

In 1910 the above method was recommended for dealing with carriers in the French Army, together with swabbing of the pharynx twice daily with glycerin containing 3 per cent iodine, and the use of a hydrogen peroxide gargle.

Dubois and Warren tested a number of antiseptics against the meningococcus and found that a mixture of ½ to 1 per cent hydrogen peroxide and 9 per cent argyrol destroyed the organism quicker than any other solution that could be used as a spray.

During the Dallas epidemic Sophian used ½ per cent hydrogen peroxide as a nasal spray and gargle; he states that in most instances this measure rendered the naso-pharynx aseptic in a few days, while more persistent carriers were usually free within ten days.

Bethege divided 60 carriers into six groups and treated each group by means of one of the following methods:

1st group	.	.	.	Pyocyanase.
2nd ,,	.	.	.	Hydrogen peroxide.
3rd ,,	.	.	.	Anti-meningococcal serum (as a spray).
4th ,,	.	.	.	Protargol.
5th ,,	.	.	.	Salt solution (1 per cent).
6th ,,	.	.	.	No treatment.

His final conclusion was that hydrogen peroxide preceded by salt solution gave the best results.

Gregor and Lindsay advised 5 per cent argyrol with 2 per cent hydrogen peroxide used twice daily as a spray.

Fairley and Stewart made use of a nasal douche of normal saline applied twice daily, together with a weak peroxide gargle. They state that very few carriers failed to give a negative swab after a week.

Foster and Gaskell employed the following solution as a nasal douche used three or four times daily: potassium permanganate (1 in 1000) in solution with 1·5 per cent sodium sulphate, the mixture being diluted with an equal quantity of water prior to use. The sodium sulphate is believed to assist penetration. They found that this mixture caused the meningococcus to disappear from the naso-pharynx, but in some cases the organism reappeared after 48 hours.

Chloramine. — More recently the substance known as chloramine T (sodium toluene-para-sulphochloramide), first prepared by Chattaway in 1905, has been used as a nasal douche in the treatment of carriers with considerable success. Chloramines are sub-

stances which contain chlorine linked to nitrogen, and almost all of which possess marked germicidal properties. Further, chloramines do not cause precipitates or coagula in secretions or in exudates, a fact which renders them of value for acting on microorganisms contained in such fluids.

We have made extensive use of a 1 per cent solution of chloramine T, the carrier being directed to sniff the liquid from the palm of his hand into the nose and return it through the mouth. This procedure is repeated several times in succession each morning and evening, the course of treatment lasting for three days and being repeated if necessary. The solution of chloramine T is made up to 2 per cent strength and diluted with an equal quantity of warm water just prior to use.

Since carriers, as pointed out previously, tend to rid themselves of the meningococcus during the fine and warm weather, only those dealt with during the winter months, that is, from the beginning of December 1916 to the end of March 1917, have been included in the following summary of results :

16 carriers were admitted.

12 of these, after three days' chloramine treatment, became negative, and subsequent swabs, after an interval of one week without treatment, failed to yield meningococci. They were therefore considered free.

2 carriers, after the same course of treatment, were found negative ; on swabbing a week later, no treatment having been given in the meantime, a positive result was obtained. Treatment was then resumed for four successive days under our personal supervision ; three further swabs, taken at intervals of five days, then proved negative.

1 case was negative after three days' treatment ; douching was then suspended. On swabbing a week later, meningococci were found to have returned. Three days' further treatment was followed by a similar result—swab negative, but positive a week later. Treatment was resumed for four days under our personal supervision, following which three swabs taken at weekly intervals proved negative.

1 carrier was still positive after the first three days' treatment. Under our own supervision the douche was resumed for the same period ; all subsequent swabs were negative.

The following case is instructive : A nursing sister came on duty in the cerebro-spinal fever ward for a few days in relief of the usual sister in charge. At the end of this period of duty her nasopharynx was swabbed and found positive. She was therefore

isolated and the routine three days' chloramine treatment ordered, the douche being performed in her own quarters. Forty-eight hours after the cessation of treatment the naso-pharynx was again swabbed with a positive result. It was then noticed that the sister had a deflected nasal septum, giving rise to complete obstruction on one side of the nose. It was certain, therefore, that little of the chloramine solution had reached the naso-pharynx. The treatment now adopted was the spraying of the post-nasal region from an atomiser fitted with a long jet, with the following solution :

Formalin	.	.	.	5 minims.
Acid Carbol.	.	.	.	5 ,,
Glycerine	.	.	.	2 drachms.
Rectified spirit	.	.	.	2 ,,
Water	.	.	.	to 1 ounce.

The application was carried out twice daily for three days by a nurse. At the end of this period the naso-pharynx was still positive, and four further days of the same treatment under the same conditions also failed to exterminate the meningococci. The patient by this time had been " carrying " for nearly four weeks. Following this failure, for three days, one of us personally syringed 1 per cent chloramine solution through the patent nostril into the naso-pharynx, causing the fluid to be expelled through the mouth. This procedure was performed both morning and evening four times for a period of three days. Twenty-four hours after the last application a swab was taken which failed to yield meningococci. Also, five further swabs taken at intervals of three or four days all proved negative.

Of cases recovering from cerebro-spinal fever during the months of December 1916 and January 1917, seven were found still to be harbouring the meningococcus in the naso-pharynx during convalescence. The following table shows the length of the period elapsing between the day of the onset of the disease and the day of taking the last positive swab prior to the application of the chloramine treatment.

2 cases	.	.	.	20 days.
2 ,,	.	.	.	6 weeks.
3 ,,	.	.	.	3 months.

The type of organism obtained in the naso-pharynx during convalescence, as tested by Gordon's univalent agglutinating sera, in each case invariably coincided with that which had been cultivated

from the cerebro-spinal fluid during the course of the disease ; also, in those patients in whom a naso-pharyngeal swab had been taken on admission to hospital, the type of organism was identical with that obtained after recovery. Further, the patients were not all infected with the same type of organism. Two yielded Type I., three Type II., and two Type III. In view of these findings the fact of cross infection having occurred is most improbable. Consequently the periods given coincide with the duration of the carrying period, which, it will be seen, is sufficiently long to have allowed the patient ample time to rid himself of the organism if he were likely to do so unaided.

Following the application of the usual three days' course of chloramine, seven of the patients became negative and no less than six remained so, for subsequent swabs, four in number and taken at weekly intervals, failed to yield meningococci. The remaining case, although proving negative at the first swab following treatment, yielded a positive result one week later. After a second course of treatment, under our personal supervision, all subsequent swabs were negative.

The conclusion from the above results is that chloramine T in 1 per cent solution and used as a nasal douche is of definite value in the treatment of carriers. Its application, however, if good results are to be obtained, must be personally supervised by the physician and not left to nurses or orderlies.

Early in 1915 Küster reported a method of treating carriers in an inhaling chamber. The disinfectant used was a hypochlorite which liberated chlorine on contact with acids. One hundred men at a time were passed through the inhaling chamber, and after three visits on three successive days the majority of the carriers were reported negative ; in only a few cases, it is said, was a further course necessary. Although the inhalation smelt strongly of chlorine, it is reported that no ill effects were observed.

Gordon and Flack, on account of the unsatisfactory reports on the treatment of persistent carriers, considered the question of conveying the disinfectant in the form of fine droplets floating in a cloud or mist, mixed with steam derived from an automatic spray, activated by high steam pressure, and in sufficient concentration to destroy the meningococcus.

After preliminary experiments with other spraying apparatus, Gordon and Flack used a special portable spray known as the

Falmouth atomiser, and designed by Lieut. E. Gordon, R.E. This apparatus atomises a disinfectant at the rate of one litre in 20 minutes over a space of 750 cubic feet, steam being the motive agent employed. Two forms of atomiser jets were used. No. 1 jet consists of a brass gas jet regulator, having a cup head into which the disinfectant is allowed to flow at the required rate ; steam escapes under pressure and blows the disinfectant out in the form of fine droplets into the surrounding air. In order to use the steam to the best advantage a cap is made to screw over the cup and press slightly on the disinfectant so as to ensure the latter flowing all round the jet of steam. No. 2 jet is very similar except that the shape of the cap produces a strong suction which pulls up the disinfectant vertically from a point 18 inches below. The copper and brass boiler is 5 by 6 inches in size, and is surrounded by sheet-iron casing which keeps in most of the heat ; it is fitted with 4 fire tubes. Directly over the boiler there is a tray partially filled with water which absorbs most of the waste heat, and also serves as boiler-feed water, being connected to the boiler by a wheel valve. The boiler is heated by a pocket primus stove which can readily be slipped in and out from under the boiler ; the latter should always be left full, filling being accomplished by allowing the steam to die down and then opening both the wheel valve and tap. As soon as the water is seen to overflow from the tap, it is at the correct level for further operation, and wheel valve and tap should be turned off. There is no steam valve on the top of this boiler, so that there is a clear passage of steam to the jet, a safety valve being placed on the tube close to the jet. Either No. 1 or No. 2 jet can be used. With the former, when steam has risen, it is necessary to turn on the disinfectant. With No. 2 jet the bottle of disinfectant is placed on the boiler base, and, after the primus has been lighted, the plant is automatic. Later, with No. 2 atomiser, a revolving jet was proposed with a view to getting better diffusion of the droplets.

In experiments with the above atomiser, Gordon and Flack used a number of disinfectants, the chief of which were chloramine T and zinc sulphate. It was found that when 5 per cent chloramine was used, the atmosphere became too pungent for comfort, but a 2 per cent solution could be tolerated easily for five minutes, and by some individuals for 20 minutes or longer. After preliminary experiments, using the streptococcus epidermidis as a control, the treatment of carriers was proceeded with. The cubic capacity

of the room in which the treatment is carried out is 750 cubic feet, and into this area, in the course of 15-20 minutes, is sprayed one litre of the disinfectant solution, the carrier remaining in the room during the whole of that time inhaling air through the nostrils. The inhalations are carried out once daily.

By such means nine chronic carriers, six of whom had been under previous treatment for periods varying from 10 to 17 weeks, were rendered negative in from 4 to 10 treatments. Three other chronic carriers failed to clear up even after 14 to 16 treatments ; of these, two did not appear to inhale properly and one was super-sensitive to chloramine. Zinc sulphate (1-2 per cent solution) was found to be tolerated rather better than chloramine, especially during the warm weather. The results, however, were not as satisfactory as those with chloramine, one chronic carrier requiring 70 inhalations before he could be discharged. Lightly infected carriers cleared up in 2 to 8 treatments, while carriers more heavily infected often required from 18 to 42 inhalations.

Recently, Dunham and Dakin have pointed out that it is prob-able that the concentration of antiseptic actually present at a given time in a spray produced by steam is insufficient to act promptly ; and since a more concentrated solution would be likely to prove irritating, it would seem necessary to prolong the time of contact without increasing the concentration. Chloramine T although soluble in water is practically insoluble in oils. The corresponding dichloramine (toluene-para-sulphodichloramine), to which the originators propose to assign the abbreviated name of Dichloramine T, though sparingly soluble in paraffin oil, is readily dissolved by eucalyptol. The resulting solution can be subsequently diluted with paraffin. Thus, a reasonably bland oily solution, con-taining as much as 2 per cent dichloramine T, can be obtained. As the above oils, however, combine with chloramine, it is neces-sary, in order to obtain a reasonably stable solution, to reduce their avidity for this element by previous chlorination.

When oily solutions of dichloramine come into contact with aqueous liquids, a part of the chloramine passes into the latter. The former serves as a reservoir from which the chloramine can be drawn to maintain a certain concentration of active antiseptic in the watery medium with which it is in contact. The experiences of Dunham and Dakin showed that the active chlorine content in the antiseptic was not exhausted after two hours when a 2 per cent solution was sprayed into the nose with an oil atomiser. Also,

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the action of the chloramine could be maintained without discomfort for a much longer period than when aqueous solutions alone were used. The action was better when the naso-pharynx was first cleansed with salt solution. The spraying should be carried out four times daily ; the first few applications may cause sneezing, but the nasal mucous membrane, according to Dunham and Dakin, appears quickly to acquire tolerance, and subsequent application causes no inconvenience.

Since many local applications cause the meningococcus to disappear temporarily from the naso-pharynx, as tested by means of naso-pharyngeal swabs, at least 48 hours should elapse between the cessation of treatment and the taking of the swab ; if a negative result is obtained, a second swab is taken after an interval of several days, the patient in the meantime remaining without treatment. If the swab also prove negative, the individual may be discharged from isolation and regarded as free.

Specific Treatment.—Colebrook and Tanner investigated the results of treating ten persistent carriers by means of active immunisation with vaccine. The doses employed ranged from 50 millions to 2000 millions given subcutaneously, and from 50 millions to 300 millions administered intravenously. As regards reaction, subcutaneous administration produced no general symptoms and only a moderate local reaction ; intravenous doses of over 100 millions gave rise to slight constitutional disturbances which, however, passed off within 12 hours. After a short time five of the ten carriers became negative, but later some meningococci reappeared ; the other five cases were unaffected.

Since the meningococcus exists in the naso-pharynx of carriers purely as a saprophyte the above results would be anticipated. The carrier does not free himself from the meningococcus by becoming immune. The serum of carriers fails to show any evidence of possessing immune bodies against the meningococcus, and further, convalescent cases, who may occasionally exhibit such reactions, are frequently found to harbour the meningococcus in the naso-pharynx.

Does an Attack of Cerebro-spinal Fever render an Individual immune from further Attacks of the Disease ?—At present there exists no definite evidence as to what degree of immunity one attack of cerebro-spinal fever confers. The following case is an example of an individual suffering from two definite attacks of the disease within 13 months :

CASE LX.—The patient, a soldier aged 21, came under our observation shortly after recovery from the second attack of cerebro-spinal fever.

First Attack.—During February 1916, on returning one day from a route march, he was seized with shivering attacks ; he vomited during the night and later was admitted to hospital in a delirious condition. For the following particulars we are indebted to Captain P. W. Maclagan, under whose care the case was admitted. The patient suffered from a definite attack of cerebro-spinal fever, the meningococcus being isolated from the cerebro-spinal fluid. Following recovery, he remained a carrier for two months, but eventually three consecutive negative swabs were obtained. The man rejoined his unit in July 1916, and proceeded to France in December of the same year.

Second Attack.—On March 5, 1917, on returning for rest after a spell in the trenches, he experienced what he described as a " shivering attack," followed by diarrhoea and vomiting. On this occasion, however, the attack of cerebro-spinal fever was apparently less severe as no delirium occurred, the patient having a clear recollection of all that took place. Lumbar puncture was performed six times, and the note that accompanied him on his return to England stated that the meningococcus had been isolated from the cerebro-spinal fluid.

Captain P. W. Maclagan also informs us that a case came under his observation, in which there appeared to have been two definite attacks at an interval of only four months.

. . . Consequently, second attacks of the disease, although rare, undoubtedly do occur.

As far as the presence or otherwise of agglutinins in the blood serum of recovered cases is an indication, the degree of immunity conferred by an attack of cerebro-spinal fever would appear to be small. In 39 recovered cases, tested at periods varying from four days to ten months after recovery, we were able to demonstrate agglutinins in the serum of three cases only (*vide* Chapter XI. p. 300, and Tables XX. and XXI.).

THE PRODUCTION OF IMMUNITY BY SPECIFIC MEASURES

Passive Immunisation.—Jochmann, in 1906, when publishing the results of his experiments on the production of a specific immune serum, mentioned the possibility of using such a serum in the prophylaxis of the disease, as, when injected, it gives rise to a passive immunity of temporary duration. In 1907 Ruppel also advised this procedure as a preventative measure, the dose recommended being 20 c.c. During the Texas epidemic of 1912 Sophian

injected anti-meningococcal serum in those individuals who were continually exposed to the disease — physicians, nurses and attendants. In no instance did the disease develop within a month after injection, this being the limit of time during which one could reasonably expect protection. One individual, a porter, developed the disease six weeks after the prophylactic dose of serum.

Among the objections to passive immunisation with serum are —the immunity conferred by serum is merely temporary, the possibility of serum sickness interfering with duties, and the danger of anaphylaxis should the infected person develop the disease and be treated with serum.

Active Immunisation.—The efficacy or otherwise of prophylactic vaccination against cerebro-spinal fever can only be determined by (1) the experimental demonstration of the presence of definite immune bodies in the blood, developing as a result of meningococcus infection and also in response to the injection of killed cultures of the organism. (2) Evidence of protection in vaccinated individuals against the disease in epidemics, especially among those who have been in intimate contact with carriers or with actual cases.

Experimental Evidence.—From time to time observers have demonstrated agglutinins, complement-fixation bodies, etc., in the blood of cerebro-spinal fever patients. Some authors—Lingelsheim, Kutscher, Krumbeim, and Schatiloff—have reported fairly uniform results, while others—Trautmann and Tromme, Eberle, Lieberknecht, Elser and Huntoon, and Arkwright—have experienced irregular and variable results with regard to the presence or otherwise of agglutinins. This lack of uniformity is in some instances, no doubt, due to using for the test a meningococcus of a different strain from that infecting the patient. This explanation, however, does not suffice to account for the very irregular results that are obtained. When using the organism isolated from the patient's cerebro-spinal fluid or one of identical serological type in testing for agglutinins, we have experienced very irregular results. Thus, of 13 patients suffering from the disease, the serum of seven showed no trace of agglutinin in dilutions of 1 : 10 or 1 : 20 ; in three, a trace was apparent in 1 : 40, but not in 1 : 80 ; the remaining three showed complete or partial agglutination in dilutions up to 1 : 80.

In 39 patients recovered from cerebro-spinal fever we tested the blood serum against either a meningococcus of the same (Gordon) type as that which had been isolated from the patient's cerebro-

spinal fluid during the attack or against the three types, and in later cases all four types. The time of testing varied in different cases from four days to ten months after recovery from the disease. Agglutinins were detected in three cases only (*vide* Chapter XI. p. 300, and Tables XX. and XXI.).

Sophian and Black, in 1912, injected ten healthy medical students with killed meningococci in the following doses :

> 5 cases received an initial dose of 500 million organisms and a second dose of 1000 million after an interval of seven days.
> 5 cases received an initial dose of 1000 million organisms and a second dose of 2000 million after an interval of seven days.

A week after the second injection the latter five cases were given a third dose of 2000 million of freshly prepared vaccine. In practically all instances a slight leucocytosis was present 24 hours after injection, the number of white cells returning to normal on the fourth day. Little or no change was noticed with regard to the differential blood count, but the degree of leucocytosis was greater after a second and third injection. In testing for the presence of agglutinins, a meningococcus was used readily agglutinable by immune sera and showing no spontaneous agglutination. The highest agglutination titre, it is stated, was yielded by those patients who had received three injections of vaccine, the larger doses apparently producing a more potent agglutinating serum than the smaller. Agglutination increased after a repeated dose of vaccine and appeared to develop to a maximum about one week after inoculation. Immune bodies were also demonstrated in these cases by complement-fixation as early as the fourth day after the first injection. The highest and sharpest fixation was present after three injections of vaccine, although high fixation up to 1 : 200 occurred at the third week after only two injections.

As a result of this experimental work, Sophian and Black concluded that very large doses of vaccine do not produce much higher immunity than smaller doses.

In animals such as rabbits, sheep and horses, there is a prompt formation of immune bodies in the blood serum, in response to the repeated injection of increasing doses of meningococci.

Clinical Evidence.—The evidence available from a clinical source is necessarily somewhat indefinite. Since the disease is apparently contracted only by susceptible individuals, the fact that so many vaccinated persons failed to develop cerebro-spinal fever

during an epidemic is not definite evidence that protection was afforded by the injection of vaccine. On the other hand, some doubt would be cast upon the value of protective inoculation if an individual so treated developed a severe form of the disease. Such evidence as is available is as follows :

Hall (1912), in Kansas City, U.S.A., inoculated 280 individuals of 50 families in which the disease had occurred. None of these persons subsequently developed the disease. Three injections were given—an initial 500 million organisms, followed by two doses of 1000 millions each.

In Dallas, Texas (1912), on Sophian's recommendation, about 100 persons were vaccinated, but as far as could be learned few, if any, received the full number of prescribed injections. Two nurses, each of whom had had two injections, developed cerebro-spinal fever some weeks after inoculation, but both recovered. With regard to these two cases, Sophian considers that in view of the fact that neither had had the full course of vaccine and that no examination of the blood was made to determine the degree of immunity produced, too much weight cannot be attached to the occurrence.

Treadgold (1915) inoculated 79 carriers, none of whom developed cerebro-spinal fever. The doses were small, consisting of a first dose of 50 millions, followed by a second of 100 millions one week later. As pointed out previously, however, the number of carriers developing the disease is very small.

Aaser (1916) inoculated some 1200 men of an infantry regiment in which cerebro-spinal fever had occurred. No vaccinated persons developed the disease. The inoculations consisted of two doses, each of 300 million organisms, given at an interval of four to five days.

Reaction to Vaccination.—Sophian found that about four hours after injection an area of inflammation consisting of redness and some swelling appeared ; this area became larger during the few hours following, and was often painful and tender. After 24 hours most of the inflammation had disappeared. As a result of the second injection, local reaction was sometimes more marked and was accompanied by an area of erythema.

In actual cases of the disease receiving vaccines we have found local reactions uncommon.

Constitutional symptoms following vaccination are often absent. Malaise, frontal headache and slight pyrexia of 24 hours' duration

occasionally develop. In a few instances intense general bodily pain, nausea and vomiting may occur, together with a rise of temperature to 102° or 103° F. Herpes is also occasionally seen. Such symptoms, however, are unusual.

Davis, after giving himself a somewhat large dose of killed meningococcus culture, experienced severe headache, chills, pyrexia, general pain and marked prostration for several days.

The soluble products of dead meningococci appear capable, though rarely, of irritating the meninges. Consequently some clinical signs of slight meningeal irritation—headache, vertigo, photophobia—may occasionally be met with following vaccine in large doses.

Objections to Protective Vaccination on a large scale that have been advanced.—(1) The possibility of the occurrence of a negative phase, immediately after the vaccine, thus rendering the inoculated individual for the time being more liable to contract cerebro-spinal fever, especially if vaccination be performed during an epidemic. Following a small dose, however, the occurrence of a negative phase sufficiently marked to allow the meningococcus to invade the system, is doubtful. Moreover, Davis, on injecting himself, found no evidence of a negative phase. Also, many carriers have been vaccinated by Sophian, Treagold and others, and none developed cerebro-spinal fever following the injection, in spite of the fact that with the organism actually present in the naso-pharynx, the danger of developing the disease during such a negative phase would appear most serious.

(2) The danger of the inoculated individual becoming a carrier of the meningococcus. This possibility, however, can be almost completely disregarded, since carriers do not harbour the meningococci in the naso-pharynx by virtue of possessing anti-bodies in their blood, and a negative phase if any after inoculation is almost inappreciable. It has previously been pointed out that the blood serum of carriers, as a rule, fails to show any definite immune properties. Consequently, there is no more risk of an inoculated individual becoming a carrier than one who has received no vaccine.

(3) The occasionally severe general and local reaction following vaccination. Severe reactions, as mentioned above, are in reality quite unusual, especially as a result of doses of suitable magnitude for prophylactic purposes.

From the above observations it will be seen that the evidence in favour of vaccination as a protective measure against cerebro-

spinal fever is by no means conclusive. Owing to the comparative unsusceptibility to the disease of most individuals, innumerable vaccinations would have to be carried out and further experimental evidence provided in order to establish the definite value of this method of prophylaxis.

If protective vaccination is decided upon, it is advisable to use the strain or types concerned in the particular epidemic. The vaccines are made in the usual manner. As regards dosage, Sophian recommends an initial dose of 500 million organisms followed by weekly injections, each dose being increased by 500 millions up to a maximum of 2000 millions.

In spite of the introduction of lumbar puncture, no appreciable diminution of the heavy mortality rate of cerebro-spinal fever was apparent until after the adoption of treatment by means of a specific anti-meningococcal serum administered intrathecally. In 1905, Flexner in America and Jochmann in Germany almost simultaneously started the experimental production of a specific immune serum. After studies on smaller animals, Jochmann was enabled to prepare his serum on a large scale by immunising horses; this serum he proved experimentally to possess both bactericidal and bacteriotropic properties. In April 1906, he reported the results of its application in the treatment of 38 cases of cerebro-spinal fever. During the course of the year the serum was used in 35 further cases, the death-rate being 27 per cent as compared with 53 per cent in those cases not treated with serum. At first the serum was injected subcutaneously, but later Jochmann advised its intrathecal administration.

The work of Flexner in America, however, has been the most important in establishing the undoubted value of anti-meningococcal serum administered by the intrathecal route. After numerous experiments on smaller animals, he immunised two large monkeys for the production of a homologous serum by means of injections of meningococci and exudate from guinea-pigs, the injections being made over a period of nine months. The animals were then bled and the serum tested. Five monkeys were given intraspinal injections of living meningococcus culture and were treated with the immune serum administered intrathecally, a control animal being used in each instance. The controls not treated with serum all died, while the other five monkeys recovered. To produce the serum on a large scale, Flexner then immunised horses. The first opportunity for its use occurred in 1907, when

an epidemic of cerebro-spinal fever appeared at Akron, Ohio ; in the serum-treated cases the mortality was 25 per cent as compared with previous death-rates of over 80 per cent.

In 1907 Kolle and Wassermann also prepared an immune serum and published the results of treatment in 57 cases of cerebro-spinal fever ; they also called attention to the great importance of early treatment. Levy, in 1908, reported further results in 33 cases treated with the Kolle-Wassermann serum, the mortality being 21·7 per cent, and later in the same year 43 cases with a mortality of only 16·2 per cent. In the same year Flexner and Jobling published records of 393 cases, 295 (75 per cent) of which recovered and 98 (25 per cent) died. In 1909 the number of serum-treated cases reached 712, with a mortality rate of 31·4 per cent. Subsequently, Flexner and Jobling issued a further report based on 1300 collected cases of all ages, 898 recovering and 402 proving fatal (mortality, 30 per cent).

The following table illustrates the mortality rate prior to the introduction of specific serum treatment compared with that of serum-treated cases :

Author.	No. of Serum-treated Cases.	Serum used.	Serum-treated Cases—Mortality.	Cases not treated with Serum—Mortality.
Flexner .	1300 (collected)	Flexner's	30·9 per cent	70 per cent
Netter .	100	,,	28·0 ,,	49 ,,
Dunn .	40	,,	22·5 ,,	70 ,,
Robb .	300 (nearly)	,,	30 ,,	72 ,,
Dopter .	402	Dopter's	16·4 ,,	65 ,,
Levy .	165	Kolle-Wassermann	18·8 ,,	52 ,,
Steiner .	2280 (collective for Texas)	...	37·0 ,,	77 ,,
Schoene .	30	Jochmann's	30 ,,	53 ,,
Sophian .	161	...	15·5 ,,	...

The striking benefit that accrued from serum treatment is further emphasised when it is recalled that the general average mortality in cases of cerebro-spinal fever varied from 70 to 80 per cent and occasionally reached as high as 90 per cent.

For instance, during the New York epidemics the figures were as follows :

1904–5	2000 cases	90 per cent died.
1906	1032 ,,	78·7 ,, ,,
1907	828 ,,	77·5 ,, ,,

In children a much diminished death-rate was also apparent.

Records were published by Dunn showing the mortality from cerebro-spinal fever occurring at the Boston Children's Hospital, before and after the introduction of serum treatment, during the eleven years (1900–1910 inclusive) that the diagnosis had been regularly confirmed by lumbar puncture. Whereas from 1900–1907 the average mortality was about 80 per cent, with the introduction of serum therapy in 1908, the average mortality for three years (1908–1910 inclusive) was 36 per cent.

In the winter of 1914–15, however, when the disease appeared extensively in Great Britain and especially amongst mobilised troops, the result of serum treatment in many places appeared far from satisfactory. Of cases occurring at Royal Naval Depôts (1914–15) the death-rate in those treated with serum was 64 per cent ; in many instances, however, the treatment was not begun until late in the course of the disease, and in others the doses appeared quite inadequate. In the Report of the Medical Research Committee on Cerebro-spinal Fever (1916), the majority of the reporters appeared unable to decide how much benefit accrued from serum and how much from the associated lumbar puncture. The average mortality seems to have been as high as 59 per cent in the serum-treated cases mentioned in this Report. In estimating the value of any report on serum treatment, it is essential to know the day of the disease on which treatment was started, the dosage, and also the frequency with which serum was given. Many of the 1915 cases did not receive treatment until comparatively late in the disease, and both the magnitude of the doses and the frequency of administration varied considerably. Also, it is probable that the disease in this country was due to strains of the meningococcus different from those used in the preparation of the anti-meningococcal serum available ; further, the quality of the latter, it is generally admitted, was not of a high standard. These facts in some measure account for the comparative failure of the serum used. Later in 1915, and since, much better serum has been available, and consequently the results for 1916 and 1917 show a considerable improvement as regards the mortality rate. Thus,

	No. of Serum-treated Cases.	Mortality.
Rolleston, H. D. (R.N. cases), August 1915–July 1916	95	31·6 per cent.
(In the first year of war the mortality in serum-treated cases was 61 per cent)		
Gray (London Military District), 1916 . .	46	21·6 ,,
Robb (Belfast), 1916–17	48	27·0 ,,

Since Gordon, in 1915, differentiated the strains of meningo-
coccus responsible for the recent epidemics in this country and
rendered their recognition possible by means of specific agglutinat-
ing sera (*vide* p. 14), these strains have been regularly employed,
notably at the Lister Institute, in the immunisation of horses for
the production of the immune serum for therapeutic use.

A more widespread knowledge of the disease and of the im-
portance of its early recognition and treatment has also served to
lower the mortality rate.

In addition to serum administration, it is essential that the
subarachnoid space should be adequately drained of its exudate.
When serum is given intrathecally, the preliminary lumbar puncture
provides the necessary drainage ; it is a frequent practice, however,
when serum administration is discontinued, to perform no further
lumbar punctures unless definite indications arise.   Formerly
this was also our own practice, but being dissatisfied with the
results obtained, especially in cases tending to run a somewhat
protracted course, we adopted routine daily lumbar puncture,
following the improvement after a certain period of serum adminis-
tration, until a perfectly clear cerebro-spinal fluid was obtained.
66 cases of the disease have come under our care since this
method of treatment was adopted, 52 of whom recovered (mortality,
21·2 per cent) ; one fulminating case, dying within 36 hours of
onset and coming under our observation only within a few hours
of death, has not been included.   Those proving fatal have in-
variably been of either the progressively purulent or the acute
fatal type, and no case has died of internal hydrocephalus.   For
the 52 cases recovering, the average duration of the course, as
estimated from the day of onset, irrespective of the day treatment
was commenced, to the day on which perfectly clear cerebro-spinal
fluid was withdrawn on lumbar puncture, was 14 days.

Production of Therapeutic Serum.—Merck's serum, as prepared
for Jochmann, was produced by injecting horses intravenously
with increasing doses of killed meningococci and later with living
cultures.   Kolle and Wassermann believed that by adding the
soluble products of the meningococcus (autolysate) to the injec-
tions, the antitoxic properties of the resulting immune serum were
largely increased.   Flexner's serum was obtained by immunising
horses with increasing doses of killed culture and autolysate injected
subcutaneously, followed by living cultures.

In a particular epidemic, cultures of the coccus isolated from

the cases concerned should be included among the strains used for immunisation. The resulting serum may then be of great value should the outbreak reappear in the following year.

The process of immunisation of the horse is somewhat slow, as serum withdrawn in less than about six months from the beginning of the injections is usually found to be very deficient in antibodies. This tardiness, however, is compensated by the fact that the immune substances once formed in the horse serum are retained for a considerable time ; one of Flexner's horses was found to yield a potent serum after a lapse of six years.

Many admirable sera are now on the market as, for example, those of the Lister, Rockfeller and Pasteur Institutes. In the majority of our own cases since December 1915 we have used the polyvalent serum supplied by the Lister Institute ; earlier results with American sera were disappointing. In the production of the Lister Institute serum, the horses have been immunised with the four epidemic types of meningococcus differentiated by Gordon ; consequently it is admirably suited for use in England.

The preservative most commonly used for anti-meningococcal serum is trikresol, of which 0·15 to 0·2 per cent is an adequate amount to prevent bacterial contamination of serum collected in a strictly sterile manner. Chloroform has also been used as a preservative and, although an efficient antiseptic, is open to objection on account of the severe pain which often follows the intrathecal administration of serum containing it. Trikresol, on the other hand, is said to have a slightly analgesic action.

Nature of Immune Substances in Anti-Meningococcal Serum.— Krauss and Dörr believed that the chief action of therapeutic serum depended upon its antitoxic properties. Flexner, Jochmann and Wassermann, however, held that although antitoxins are important constituents, the chief value of the serum lies in its bacteriotropic action. There is evidence, in vitro, of the presence of bacteriolysins, opsonins, anti-endotoxins and also agglutinins, precipitins and complement-fixation bodies. It must be recognised, however, that the presence of some of these substances may have no necessary relation to the therapeutic value of the serum. Of their relative importance nothing really definite is yet known.

Standardisation of Serum.—An accurate method of standardising anti-meningococcal serum has yet to be found. Various tests,

however, have been employed in attempting to determine the therapeutic value of a given brand of serum.

(1) *Opsonic Test.*—Flexner and Jobling, having found other tests inaccurate and unreliable, employed the opsonic test as a measure of the therapeutic activity of a particular serum. They proposed, as a definite and suitable standard of strength, a minimum dilution activity of a 1 : 5000 dilution of the immune serum. Neufeld's method was used in the test. Sophian, however, advances the following serious objections to the opsonic test ; (*a*) Irregularity and inaccuracy in readings of all opsonic work ; (*b*) the fact that the meningococcus family comprises a number of various strains, each strain reacting differently with the autogenous serum and the sera of other members of the group.

(2) *Complement-Fixation Test.*—The complement-fixation test was used by Kolle and Wassermann in the standardisation of their serum. Sophian, in estimating the value of the different tests, found that when using a meningococcal antigen and the usual haemolytic system, complement-fixation gave fairly uniform results. Control experiments made with normal horse serum showed some fixation in low dilutions, while in controls with other immune sera—anti-tetanic, anti-diphtheritic and anti-streptococcal—fixation was either absent or occurred only at equally low dilutions. An anti-gonococcal serum of high immunity, however, gave fixation with a meningococcal antigen in a dilution as high as that of anti-meningococcal serum. This, therefore, would suggest that the test is not absolutely specific, and invalidates its use as means of diagnosis but does not affect readings when working with known ingredients (*e.g.* meningococcal antigen and serum). These experiments were carried out prior to the recommendation by Schwartz and M'Neil of a standard antigen for the complement-fixation test.

In a comparison made between the opsonic and complement-fixation tests, using identical materials, Sophian found that the two tests corresponded in every instance, a high opsonic reading accompanying a high complement-fixation reading and *vice versa.* As this observer points out, however, it does not necessarily follow that in development the various immune substances go hand in hand or are dependent upon one another ; in fact, as shown by other investigators working with different sera, this is often not the case.

From the results he obtained, Sophian concludes that the thera-

peutic activity of the immune serum depends to a large extent upon the presence of opsonins, but suggests that in estimating the value of a given therapeutic serum, both the opsonic and complement-fixation tests should be employed, the former as a control and the latter for more accurate readings.

(3) *Agglutination Test.*—Since four types of meningococcus, recognisable by their reactions with specific monovalent sera, were identified by Gordon as being responsible for the recent outbreaks of cerebro-spinal fever in England, agglutination tests have largely been used in attempting to estimate the potency of therapeutic sera.   It is not definitely known what part is played by agglutinins in overcoming infection ; according to the animal-protection tests of Hitchens and Robinson (*vide* p. 400), it does not necessarily imply that a serum rich in agglutinins and complement-fixation bodies has marked ability to protect an animal against a fatal meningococcus infection.   As a high agglutination titre, however, usually accompanies strong complement-fixation power and a high opsonic index, it is safe to assume, within limits, that a serum possessing these characteristics is fairly rich in antibodies, and at least likely to prove of more value than one which fails to show any agglutinating properties towards meningococci.

From time to time we have determined the agglutination reactions of meningococci isolated from cases of cerebro-spinal fever against the anti-meningococcal serum used in treating the patients concerned, and, for purposes of estimating the general potency of the serum, also against stock cultures of Types I.-IV. cocci (Gordon).   Since the final test of efficiency of an immune serum is its efficacy in overcoming infection in the human subject, it is of value to compare the agglutination reaction of a given serum with its therapeutic effects.   On the whole, we found that a serum showing marked agglutinating power towards the meningococcus gave good clinical results.   We must admit, however, that excellent results, even in acute cases, have been obtained with sera which on subsequent testing showed little or no agglutination when put up against each of the four types of meningococcus.   Nevertheless, we consider it preferable, in the present state of our knowledge, to discard those sera exhibiting a low or absent agglutination titre towards Gordon's four types, unless the serum used for a particular patient shows good agglutination towards the one type isolated from his cerebro-spinal fluid.

The following results serve to illustrate our findings :

Case (recovering) treated with Serum showing a high Agglutination Titre.—Treatment begun on 2nd day. Organism = Type III. (Gordon) meningococcus, isolated from cerebro-spinal fluid on the second day. Serum used = Lister Institute, Series 31 B.

Agglutination Tests.—Serum 31 B against coccus (Type III.) isolated from patient = Dilutions 1 : 50 + ; 1 : 100 + ; 1 : 200 + ; 1 : 400 + ; 1 : 800 + ; 1 : 1000 negative. The patient had quite recovered by the twelfth day of illness. 150 c.c. of serum in 30 c.c. doses were given (2nd-6th day inclusive). Serum 31 B against stock cultures of the four types :

Type	I.	Dilutions	1 : 50 to 1 : 1000	positive ; negative in higher dilutions.
	II.	,,	1 : 50 to 1 : 500	positive ; negative ,, ,,
	III.	,,	1 : 50 to 1 : 700	positive ; negative ,, ,,
	IV.	,,	1 : 50 to 1 : 700	positive ; negative ,, ,,

It was concluded that 31 B serum was of considerable therapeutic value.

Another severe case yielding a Type II. organism was also treated with 31 B serum and recovery resulted. Agglutination of the organism (Type II.) isolated from the patient proved positive in all dilutions of 31 B serum, even to 1 : 2000.

Two other sera (32 A and 32 B) showed only partial agglutination in no higher dilution than 1 : 50 with each of the four types. Nevertheless, several acute cases made good recoveries with its use.

(4) *Animal Protection Test.*—By preparing a quantity of meningococcus emulsion, the protective power of the serum may be tested on guinea-pigs. The fatal dose of the emulsion having been determined, a definite quantity of the immune serum is mixed with varying amounts of bacterial emulsion and the resulting mixture inoculated intraperitoneally. Thus, when this procedure is repeated several times with the necessary controls, a rough idea of the protective power of the serum can be obtained, but the results are somewhat irregular. This is accounted for by the fact that the resistance of different animals varies considerably ; Sophian found that one guinea-pig may live when given twice the dose of meningococcus emulsion that kills another guinea-pig of the same approximate age and size. Also, as pointed out by Jobling, the pathogenicity of the meningococcus may vary from day to day.

More, recently, Parker Hitchens and G. H. Robinson (1916) have described a method of employing the animal-protection test with mice. Fresh guinea-pig serum is taken and diluted to four times its volume with 0·85 per cent salt solution ; in 1 c.c. of this

mixture a 16-hour culture of meningococci from one agar slope is then suspended. 0·5 c.c. of this suspension is injected intra-peritoneally into a white mouse; to the remaining half of the suspension 0·5 c.c. guinea-pig serum is added, half this mixture is injected into another mouse and so on. The doses received by different mice are, therefore, as follows: 0·5, 0·25, 0·12, 0·06 and 0·03 c.c. With the culture used, it was found that a mouse weighing 11 gms. and receiving 0·06 c.c. of suspension died, while another mouse of the same weight and receiving 0·03 c.c. survived. The serum to be tested is injected intraperitoneally, 0·5 c.c. in quantity, two hours before the injection of the culture. With four samples of W. K. Mulford's serum, Hitchens and Robinson obtained the following results:

(D. = Died.)

Amount of Agar Slope Suspension injected.	Sera.				Normal Serum.	No Serum.
	2059	2308	2526	2813		
0·5 c.c.	D. 24 hrs.	D. 24 hrs.	D. 20 hrs.	D. 20 hrs.	D. 20 hrs.	D. 20 hrs.
0·25 c.c.	Lived	Lived	D. 20 ,,	D. 24 ,,	D. 40 ,,	D. 20 ,,
0·12 c.c.	Lived	Lived	D. 48 ,,	D. 20 ,,	D. 24 ,,	D. 24 ,,
0·06 c.c.	Lived	Lived	Lived	D. 24 ,,	D. 20 ,,	D. 48 ,,
0·03 c.c.	..	..	..	..	D. 24 ,,	D. 24 ,,

Horse 2059 had been under immunisation for 16 months, 2308 for 12 months, 2526 for seven months and 2813 for three months. Two weeks later the sera of both 2526 and 2813 protected against 0·12 c.c. of culture.

Hitchens and Robinson found that a high agglutination titre and complement-fixation power does not necessarily imply ability to protect against fatal infection. They consider that the animal-protection test is more parallel to the extent of immunisation than either the agglutination or complement-fixation test, and further, that if the amount of serum necessary to protect against one minimum lethal dose of culture is taken as the unit, a rational and uniform method of standardising anti-meningococcal serum can be obtained. Until members of the meningococcus family have been more definitely referred to type strains, however, it is difficult to adopt a uniform method of standardisation, as a serum protecting against one type might be relatively impotent against another.

(5) *Anti-Endotoxin Test.*—The anti-endotoxin value of samples of anti-meningococcal serum has been determined by Dopter,

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Wassermann and Krause and others. Dopter, who used autolysate for the purpose, considered that 1 c.c. of anti-meningococcal serum suitable for clinical use should neutralise five minimum lethal doses of endotoxin. Krause, Wassermann and Leuchs, who used "shake extracts"—that is, solutions of endotoxin extracted from young cultures of meningococci suspended in distilled water or decinormal soda solution, by agitation for several days in a shaking machine—stated that 1 c.c. of anti-meningococcal serum suitable for therapeutic use should neutralise four lethal doses of meningococcus endotoxin. Gordon points out, however, that the anti-endotoxin standard laid down for anti-meningococcal serum by these observers is very low in comparison with the anti-endotoxic values obtained by Besredka in the case of sera prepared against B. dysenteriae, B. pestis and B. typhosus. The relative scarcity of anti-endotoxin, he suggests, most probably lies in the form of meningococcus antigen used for preparing the horses concerned.

Gordon, by adapting to the meningococcus Besredka's method of extracting endotoxin, was able to test anti-meningococcal sera in respect of their content of anti-endotoxin. His procedure for extracting the endotoxin is described on page 20 (Chapter II.).

Method used by Gordon for estimating the Anti-endotoxin Content of Anti-meningococcal Serum.—All sera examined are in duplicate, and normal horse serum is used as a control. Two sterile watch-glasses, each enclosed in a Petri dish, are taken for each serum. With a 1 c.c. pipette, graduated in tenths, the M.L.D. of endotoxin is measured out into each watch-glass (the M.L.D. is previously determined in duplicate, being taken as the lowest dose of the aqueous extract to which each of two mice succumbs within 48 hours ; the dose varies from 2 to 10 mg.). A measured amount of serum is then added, the covers are replaced and the Petri dishes incubated for 30 minutes at 37° C. in order to allow the endotoxin and anti-endotoxin to unite. When taken out of the incubator, many of the sera are seen to have produced an excellent precipitin reaction, which, however, by no means necessarily implies the presence of anti-endotoxin. The contents of the watch-glasses are then injected intraperitoneally, each into an individual mouse. The mice are kept under observation for three days.

By applying this method of testing to several samples of anti-meningococcal serum in therapeutic use, Gordon found that a certain proportion failed to show an appreciable amount of anti-endotoxin for one or other of the two commonest types of meningococci—Types I. and II. In conclusion, this observer states : " As the cause almost certainly lies in the kind of antigen used for pre-

paring the horses, a series of observations is now in progress for the purpose of defining the relative value of various preparations of the meningococcus for stimulating the production of anti-endotoxin."

Importance of Early Treatment.—Early treatment in cerebro-spinal fever is of paramount importance. All observers have found that the earlier treatment is begun the better are the results. Its great importance cannot be shown fully by statistics, as Gardner Robb points out, because in every considerable number of cases there must occur some of a fulminating type, which die within 12-48 hours, treatment having little or no effect.

The following table of 58 consecutive military cases, in whom treatment was commenced on the first to fourth day, illustrates the effect of early treatment on mortality. One fulminating case dying within 36 hours of the onset of illness is excluded.

Day of Disease on which Treatment was commenced.	Number of Cases.	Deaths.	Recoveries.	Mortality.
First day . .	5	0	5	0
Second day . .	24	5	19	20·8 per cent
Third day . .	20	7	13	35 ,,
Fourth day . .	9	3	6	33·3 ,,

Cases surviving the fifth day or later without treatment are usually subacute ; they may respond quickly to treatment or may run a protracted course. Survival of the first week, however, does not afford any greater assurance of ultimate recovery. This has been shown by Flexner as follows :

Of 1481 fatal cases—
    25 per cent died in the first 3 days.
    24   ,,   on 4th to 7th days.
    50   ,,   later than the 7th day.

When first performing lumbar puncture on a suspected case, if the cerebro-spinal fluid shows any turbidity, it is advisable to administer serum at once without waiting for the bacteriological examination. This, as far as possible, has invariably been our practice ; valuable time is saved, and no harm can be done by the serum to a possible case of pneumococcal or tuberculous meningitis.

Treatment during the Pre-Meningitic Stage.—Cerebro-spinal fever is rarely diagnosed until symptoms of meningitis develop. In cases in which the disease is strongly suspected—especially on account of the presence of a petechial or purpuric rash—and the

cerebro-spinal fluid is found clear, anti-meningococcal serum should be administered intravenously or intramuscularly, preferably the former. Doses up to 200 c.c. may be given ; Herrick, indeed, advises doses up to 600 c.c., the resulting serum rash apparently being no more severe than with the smaller amounts.

In some cases at the onset the initial shock and consequent collapse may be extremely severe. This should be combated by the application of hot bottles and rectal or subcutaneous injections of normal saline solution at a temperature of 100° F. Camphor (grs. 5) injected subcutaneously in the form of Curschmann's solution, and repeated if necessary, may also be of assistance.

If there be any question as to whether infection has reached the meninges, such as indicated by a considerable increase in the tension of the cerebro-spinal fluid, serum should be given intrathecally. Intrathecal injection at this stage often results in an aborted attack of the disease.

THE INTRATHECAL ADMINISTRATION OF SERUM

Reason for Intrathecal Administration.—Owing to the fact that the meningococcus produces its pathogenic effects by direct and local action on tissues, the full power of the anti-meningococcal serum can only be exerted when the immune principles on which these effects depend are brought into contact with the organism in a concentrated form. In the presence of meningitis, therefore, serum injected subcutaneously or intravenously is useless ; not only does it undergo an extremely high dilution in the blood stream, but there is considerable doubt if it ever reaches the subarachnoid space at all. Dixon and Halliburton and others have shown that although the lining membrane of the subarachnoid space is permeable to substances passing from the cerebro-spinal fluid to the blood, it appears quite impermeable, excepting in the case of a few drugs (e.g. hexamine) and oxygen, in the reverse direction— from blood to cerebro-spinal fluid. The nutritive materials contained in the cerebro-spinal fluid are probably formed in the choroid plexus and not merely exuded from the blood stream ; otherwise, it is not possible to explain why the protein contained in the cerebro-spinal fluid is not similar to that of the blood or of exudate formed from the blood. The choroidal epithelium is a stalwart barrier of secretory cells which keeps back even readily diffusable substances, and allows only the normal secretion to escape.

The absorption of immune bodies from the cerebro-spinal fluid into the blood stream, however, is fairly rapid. Debré, by means of the sensitive precipitin reaction for a foreign serum, showed that the reaction appeared in the blood about 10 minutes after the intrathecal injection of the foreign serum. Hohn, by determining the content of the cerebro-spinal fluid, found that the serum for the most part is absorbed within 24 hours.

Consequently, it is evident that for the anti-meningococcal serum to exert its maximum effect, it must be introduced directly into the subarachnoid space, and in order to make good the loss in concentration sustained by its absorption into the circulation, at intervals of not longer than 24 hours.

Summary of Treatment adopted by Authors.—A summary of the treatment we have adopted is as follows : Serum is given intrathecally at the earliest possible moment without waiting for the bacteriological report, the initial dose being 30 c.c. This amount is then administered daily, or occasionally twice daily, until the clinical improvement is quite definite and undeniable and organisms, if previously present, have disappeared from the cerebro-spinal fluid. Owing to the fact that, occasionally, meningococci may neither be seen in nor cultivated from the cerebro-spinal fluid obtained by lumbar puncture when clinical symptoms are well marked, the bacteriological findings are inclined to be misleading if relied upon solely. On post-mortem examination, it is not unusual to discover meningococci in the ventricles, when they have been absent from the cerebro-spinal fluid obtained by lumbar puncture for some days before death.

The minimum period for the continuance of serum administration is four days, no matter how great the improvement in the patient's condition may appear ; the merely apparent improvement so often observed on the second or third day is thus covered. The dose is always 30 c.c., excepting when it is possible only to obtain less than this quantity of cerebro-spinal fluid ; in such a case the fluid withdrawn should exceed the amount of serum injected by at least 5 c.c. A few exceptions to this rule will be mentioned later.

When the clinical improvement is quite decided and meningococci have disappeared from the cerebro-spinal fluid, serum administration is omitted, lumbar puncture alone being performed and repeated daily until the cerebro-spinal fluid is clear to the naked eye, there being no symptoms of hydrocephalus. Should any sign of a recrudescence of meningitis occur during the period of

26 a

repeated daily lumbar puncture, particularly mental relapse, increased turbidity of the cerebro-spinal fluid or reappearance of meningococci, serum administration is recommenced and continued on the same lines.

Vaccines are also employed, their use being considered of chief value in the later stages of the disease. Administration begins within the first three days of treatment with an initial dose of 250 million organisms ; doses are then given every fourth day, each dose increasing by 250 million organisms up to 500 millions and afterwards by 500 millions up to 2500 millions. Indications for a departure from this routine dosage are dealt with in the detailed consideration of vaccine treatment (p. 428).

Lumbar Puncture

Lumbar puncture appears first to have been performed by Corning in America, in 1885, for the purpose of injecting cocaine intrathecally. Four years later Wynter, in England, punctured four cases of tuberculous meningitis for the relief of cerebro-spinal fluid pressure. In 1890 Quincke studied the operation fully, and it is largely due to his work that it was eventually introduced as a routine clinical measure.

Anatomy of Cauda Equina and Associated Subarachnoid Space.—At the lower part of the spinal canal, where the arachnoid is closely applied to the dura mater, the subarachnoid space is considerably more spacious than in the upper part ; through this portion of the cavity pass the spinal nerves forming the cauda equina. During the first year of life, the spinal cord usually extends slightly beyond the lower level of the third lumbar vertebra, but owing to the relatively rapid growth of the spinal column, the cord gradually recedes and in adults seldom reaches lower than the first lumbar vertebra (*vide* Fig. 43).

FIG. 43.—Diagrammatic representation of the subarachnoid space in the lumbar region (lateral aspect).

L₁-L₅ = lumbar vertebrae ; c.m. = conus medullaris ; s.s. = subarachnoid space ; f.t.i. = filum terminale internum ; f.t.e. = filum terminale externum.

The distribution in the subarachnoid space of the nerve roots forming the cauda equina may vary considerably, but the general

order of arrangement in relation to one another is fairly uniform. They arise serially from the conus medullaris and pass downwards in regular order in a vertical row, on each side of the spinal canal, to their respective foramina of exit. Thus, the first lumbar nerve has the highest and most lateral origin from the conus medullaris ; the second lumbar root arises below the first and so on, until almost from the apex of the conus, the lowest sacral nerve roots originate. The latter nerves, therefore, occupy the most mesial position of all, lying either in close relationship with or diverging a little from the mesial sagittal plane.

Lusk, in a series of fifteen dissections, carefully studied the anatomical relations of the cauda equina. He found that when the nerve-roots lay together in masses, they did not individually float free in the cerebro-spinal fluid but were bound together by delicate adhesions, which, though capable of being broken apart with little or no force, were nevertheless sufficiently strong to hold the roots together as one solid structure. Occasionally the nerve-roots were found to float

Fig. 44. — Diagram of transverse section through the spinal canal at the level of the fourth lumbar intervertebral space, illustrating the position of the spinal nerve-roots.

v.t.c. = vertebral canal ; d.a. = dura-arachnoid ; s.s. = subarachnoid space ; n.v.r. = nerve-roots ; t. = trabeculae.

freely, but only in the lower part of the subarachnoid space below the position of the main mass.

Above the level of the fifth lumbar vertebra, Lusk found that the laterally situated nerve-roots were firmly adherent to the arachnoid, while the latter membrane usually lay loosely over the posterior surfaces of the more medially situated nerve-roots, being connected to them by delicate trabeculae varying from $\frac{1}{8}$ to $\frac{1}{4}$ inch in length, the shorter trabeculae occupying the more lateral position (*vide* Fig. 44). Below the level of the fifth lumbar vertebra all the nerve-roots were adherent to the arachnoid.

Apparatus.—The lumbar puncture needle is about 10 cms. long, 1·5-2 mm. in diameter, and should be provided with a well-fitting stylet with a short, bevelled extremity coinciding exactly with that of the needle.

Site of Puncture.—The interspace between the fourth and fifth lumbar vertebrae is the site usually selected for puncture, as here

the subarachnoid may be entered well below the conus medullaris and the nerve-roots are least liable to injury. The lumbo-sacral space is equally suitable, although in this situation there is a greater tendency for the nerve-roots to become adherent to the posterior part of the arachnoid, as well as for the subarachnoid space to be somewhat more shallow ; practically, however, difficulties seldom arise. It appears probable, according to the observations of Lusk, that on puncturing the fourth lumbar intervertebral space, when the needle is not too sharp, the dura yields before the pressure of the needle-point ; consequently, a wedge of dura is driven into the subarachnoid space, thus clearing a path between the nerve-roots which recede on either side before the arachnoid gives way (*vide* Fig. 45).
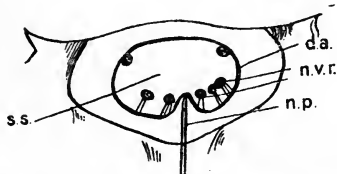
FIG. 45.—Diagram of transverse section through the spinal canal at the level of the fourth lumbar intervertebral space, illustrating the manner in which a wedge of dura is probably driven in by the spinal needle and the nerve-roots pushed on either side before the theca is penetrated.

d.a. = dura-arachnoid ; s.s. = subarachnoid space ; n.v.r. = nerve-roots ; n.p. = spinal needle.

In repeating lumbar punctures, the interspace entered should if possible be varied from day to day, as, if too frequent puncture be performed at the same spot, adhesions may form and shut off the underlying subarachnoid space. In the presence of strict asepsis the skin wounds never cause any trouble.

As regards puncture at higher levels than the fourth lumbar interspace, although less desirable on theoretical grounds, in practice lumbar puncture may be performed, if necessary, up to the first lumbar interspace, that is, between the first and second lumbar vertebrae. When no fluid can be obtained at the lower interspaces, we have frequently punctured as high as this level without any harmful effect. In one case developing marked symptoms of hydrocephalus no fluid whatever was obtainable at or below the first lumbar interspace. On puncturing between the 1st lumbar and 12th thoracic vertebrae, care being taken not to penetrate too deeply, 40 c.c. of cerebro-spinal fluid were obtained ; subsequently, the interspace between the 11th and 12th thoracic was entered without appreciable ill effect. The patient was incontinent throughout his illness, but finally recovered on about the 40th day ; incontinence of urine was almost the last symptom to disappear, normal control being established by the 46th day. In this case, therefore,

it cannot be certain whether the incontinence was due to puncture at such a high level or to the disease itself. Sophian has encountered incontinence after puncture at about the first lumbar interspace, but could not be certain that it was not due to the meningitis ; it invariably disappeared early in convalescence.

Above the level of the 11th thoracic vertebra, puncture is practically useless. In a series of 11 dissections Lusk found that in only three was there present a complete posterior subarachnoid space above the conus medullaris. Gerstenberg and Hein had previously shown that the spinal subarachnoid space was divided by the ligamenta denticulata into an anterior portion and a posterior
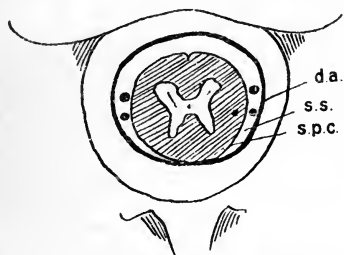
FIG. 46.—Diagram of transverse section through the spinal canal in the thoracic region, illustrating the posterior aspect of the spinal cord adherent to the dura-arachnoid. (Modified from Lusk.) In six out of ten dissections, Lusk found this to be the predominating arrangement in the thoracic and lower cervical regions.

d.a. = dura - arachnoid ; s.s. = subarachnoid space ; s.p.c. = spinal cord.
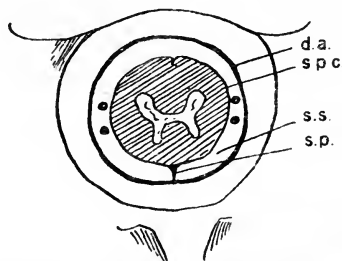
FIG. 47.—Diagram of transverse section through the spinal canal in the thoracic region, illustrating the presence of a posterior subarachnoid space. The spinal cord is connected with the dura-arachnoid by a fibrous septum. (Modified from Lusk.) In three only of eleven dissections was this anatomical feature found by Lusk.

d.a. = dura-arachnoid ; s.s. = subarachnoid space ; s.p.c. = spinal cord ; s.p. = septum.

portion, each communicating with the other through the spaces between the denticulations of the ligament ; in the three of Lusk's dissections which showed the presence of a complete posterior subarachnoid space, interrupting transverse septa occurred at intervals, so that the channel was not continuous. Free circulation of cerebrospinal fluid, however, was allowed by means of the lateral communications with the anterior part of the space through the ligamentum denticulatum. In the remaining eight dissections, adhesions existed at various sites between the spinal cord and the posterior portions of the arachnoid (*vide* Fig. 46). The adhesions extended downwards to a distance varying from the level of the fifth thoracic vertebra to two inches above the conus medullaris.

From these observations it will be seen that it is an unsafe procedure to perform intervertebral puncture at any level higher than two inches above the conus medullaris as there can be no certainty of the presence of a posterior subarachnoid space ; cerebro-spinal fluid could only be obtained constantly by traversing the substance of the spinal cord and withdrawing it from the anterior part of the subarachnoid space.

The Question of Anaesthesia.—There is some difference of opinion concerning the advisability of administering a general anaesthetic for the performance of lumbar puncture. One of us, having performed many hundreds of punctures in routine neurological work, does not consider an anaesthetic at all necessary as a general rule ; it is of course essential in tetanus, but in cerebrospinal meningitis we have used general anaesthesia on only three or four occasions when the patient has been particularly violent. Provided one has a competent assistant with a thorough knowledge of the requisite position in which to hold the patient, the operation is performed without difficulty, always allowing moderate skill on the part of the operator.

Patients, when conscious, do not often complain of the actual puncture when it is rapidly performed and the canal entered at the first attempt ; as an example, two military cases, suspected of being mild cases of cerebro-spinal fever, were admitted, having been punctured elsewhere under general anaesthesia. When the operation was performed without an anaesthetic, they stated afterwards that they would not have had the previous anaesthetic had they known the operation was so slight and accompanied by so little pain.

Further, an anaesthetic in meningitis is not altogether free from risk ; it occupies more time and when given daily may interfere considerably with the patient's nourishment.

The question of local anaesthesia need scarcely be considered, as the pain due to penetration by the lumbar puncture needle is seldom felt, once the skin has been pierced, unless the bone be struck ; if the lumbar puncture is properly carried out, this should not occur. Consequently, the patient is not likely to experience any more discomfort from the passage of the spinal needle, in the hands of a competent operator, than from the skin punctures necessary for the injection of the local anaesthetic.

Position of the Patient.—The patient is brought to the edge of the bed or table in the left lateral position (when the operator

is right-handed), the spine being arched forwards as much as possible by flexion of the head and legs. The position is maintained by an assistant kneeling on the bed in front of the patient, one arm encircling his knees and the other his neck ; the assistant should endeavour to clasp his two hands together in order to prevent any sudden straightening of the back on the part of the patient. Three or four pillows are placed under the patient's head in such a way that the body slopes at an angle of about 30°-40°, thus facilitating drainage by bringing that part of the subarachnoid space where puncture is performed to the lowest level (Plate VII.).

It is almost needless to add that the strictest surgical asepsis must be maintained, all apparatus being previously sterilised by boiling, and the skin at the site of the puncture cleansed by the application of an antiseptic. For this purpose we have found ether quite satisfactory.

Method of Puncture.—Lumbar puncture may be performed by one of two routes—(1) Lateral, (2) Median.

Lateral Route.—The advantage claimed for this method is the avoidance of the thick interspinous ligament. A point is selected just lateral to the finger-tip placed on the interspinous interval, and the puncture made with the needle directed slightly upwards and inwards. Two resistances are encountered—the ligamentum subflavum and the dura mater. By this lateral method, however, the needle can very easily get out of control, and a mistake in direction at the skin is magnified when the point reaches the level of the ligamenta subflava. Thus, the needle may penetrate the interspinous ligament and impinge on the lamina of the opposite side, or it may strike the under margin of the spinous process of the vertebra just above.

Median Route.—By this route the method is simple and a considerable degree of skill is rapidly acquired, thus saving the annoyance of repeated unsuccessful attempts at puncture. With the forefinger of the left hand on the crest of the ilium and the thumb defining the interspinous space opposite the finger, the needle is pushed in perpendicular to the median line (*vide* Fig. 48 and Plate VII.). As a small tubercle projects downwards from the lower margin of the upper spinous process, it is well to follow as closely as possible the upper edge of the lower spinous process. It is essential to be quite certain that the point of the needle is exactly in the mid-line of the space, and the shaft perpendicular to the skin surface. If the needle is maintained in this position during

penetration no mistake can be made. We have almost invariably used the median method and consider it undoubtedly the more certain in results, especially when, as most frequently is the case, there is marked rigidity of the spine. No serious difficulty has ever been encountered in our experience.

Depth of Puncture.—For adults, Quincke estimated the depth of puncture as varying between four and six centimetres. There is, however, no consistency in the depth to be penetrated, and its estimation is of no practical value. With experience, the sense of touch, as the different strata are penetrated, affords the necessary information ; a distinct " give " is usually felt as the subarachnoid space is entered.

Amount of Cerebro-spinal Fluid evacuated.—The theca having been penetrated, the cerebro-spinal fluid is allowed to escape into a sterile graduated tube (Plate VII. B). The quantity of fluid withdrawn should be practically the maximum that can be obtained — that is, the fluid is allowed to escape until it flows through the needle at about the rate of one drop in five seconds ; we have never seen the slightest misadventure follow this complete evacuation. In cerebro-spinal fever the amount of fluid obtainable varies from 30 to 100 c.c., and occasionally reaches 120 c.c.
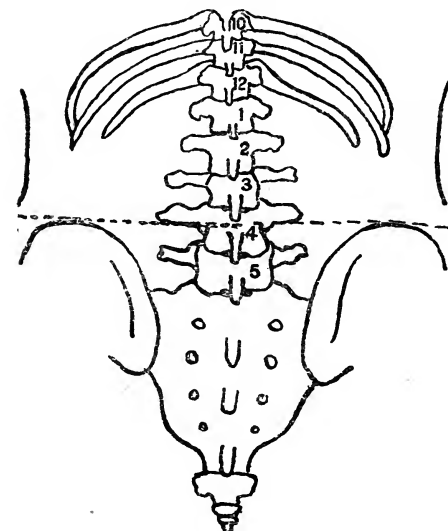
Fig. 48.—Lumbar puncture. Diagram of skeleton in lumbar region, illustrating the bony landmarks used in performing lumbar puncture (*vide* p. 411).

In observations taken of the blood pressure before, during, and after evacuation of considerable amounts of cerebro-spinal fluid, we have never met with a case showing more than a few millimetres fall in blood pressure after the withdrawal of even 60 c.c. of cerebro-spinal fluid. Often, indeed, there is no alteration, while in some cases an actual rise in blood pressure of a few millimetres is recorded (*vide* Chapter XI.).

Difficulties that may be encountered during Lumbar Puncture.—
Failure to enter the Spinal Canal.—By the lateral route, this occur-
rence has already been mentioned. If no fluid flows even when
puncture by the mesial route is performed, the needle should be
entirely withdrawn and reinserted ; it is seldom of any use merely
to withdraw it from beyond the laminae and probe.

Apparent Obstruction of the Puncture Needle.—On entering the
spinal canal the needle may appear partly obstructed, the fluid
only escaping drop by drop. This may be due to a variety of
causes :

(1) The needle, especially if possessing a very sharp point, may
pick up one of the roots of the cauda equina which partially obstructs
the orifice of the needle. In this case, rotation of the needle or
pushing it on to a slightly greater depth will establish a good flow.

(2) The dura and underlying arachnoid may only partially be
pierced, the orifice of the needle looking downwards. Similarly,
rotation and a slight onward push will rectify matters.

(3) It was pointed out when describing the site of lumbar
puncture (p. 408) that, during its passage, the needle may drive a
wedge of dura mater into the subarachnoid space before actual
penetration takes place (Fig. 45). If the dura be lax, it may be
pushed inwards to a considerable depth by the needle before being
pierced. When this occurs, as pointed out by Foster, the orifice
of the needle would lie in a narrow chink between the closely
approximated dorsal and ventral aspects of the arachnoid. If
the interval between the approximated surfaces be widened by a
slight withdrawal of the needle, a good flow is established.

(4) The subarachnoid space, as shown elsewhere (p. 355), is not
a simple cavity but is divided up into compartments by the lateral
ligamenta denticulata and occasionally by a posterior septum or
adhesion, as well as to some extent by trabeculae connecting the
roots of the cauda equina with the arachnoid. Under normal
conditions there is free communication between the loculi so formed,
but, as Horder suggests, in meningitis such communications may be
interfered with, owing to the presence of plastic exudate and
adhesions. If at first the needle enters only a small loculus instead
of the main space, the fluid would flow very slowly and might soon
cease. In such an instance, if pushing the needle a little deeper
does not increase the flow, it is advisable to withdraw the needle
and puncture again in a different interspace.

(5) A flake of purulent exudate may actually block the needle

while the fluid is flowing. By passing the stylet two or three times into the needle, kept in situ, the obstructing material will be removed.

To summarise : If the fluid only escape drop by drop, the needle should be rotated and pushed slightly further inwards—(1) and (2). If this fails to establish a satisfactory flow, the needle should be slightly withdrawn—(3). Should the needle still appear to be obstructed, the stylet should be passed two or three times ; if the desired result is not then obtained, the needle must be entirely withdrawn and a fresh puncture made in a different interspace.

Haemorrhage occurring during Lumbar Puncture.—This subject has already been dealt with in the section concerning Cerebro-spinal Fluid (Chapter X. p. 241).

Dry Puncture.—When no fluid is obtainable upon lumbar puncture, the occurrence is sometimes referred to as a " dry tap." The causes of " dry tap " are :

(1) The needle has not entered the subarachnoid cavity but remains outside the dura or else is lying at the side of the vertebra.

(2) Complete obstruction due to one of the causes mentioned above as being responsible for partial obstruction.

(3) Inflammatory exudate too thick to flow, *e.g.* towards the end of the course in cases of the progressively purulent type.

(4) The presence of hydrocephalus, either internal by the obstruction of the foramina of Magendie and Luschka, or external, the upper part of the subarachnoid space being separated from the lower by adhesions between the arachnoid and the spinal cord. In some cases the obstruction may occur at the level of the foramen magnum.

Dry puncture should not be assumed until the subarachnoid space has been entered in at least three different intervertebral spaces.

Accidents during Lumbar Puncture.—Occasionally during the operation of lumbar puncture, the patient may experience a sudden and sharp pain shoot down his thigh and leg ; this only means that the needle has touched one of the roots of the cauda equina *en route* and is of no significance.

Sometimes, in a patient so disposed, incontinence of faeces may occur as the needle penetrates the theca. This is due no doubt to the sudden stimulation of the 3rd and 4th sacral nerves, which supply the sphincter ; their mesial position renders them liable at times to come into contact with the needle during its passage.
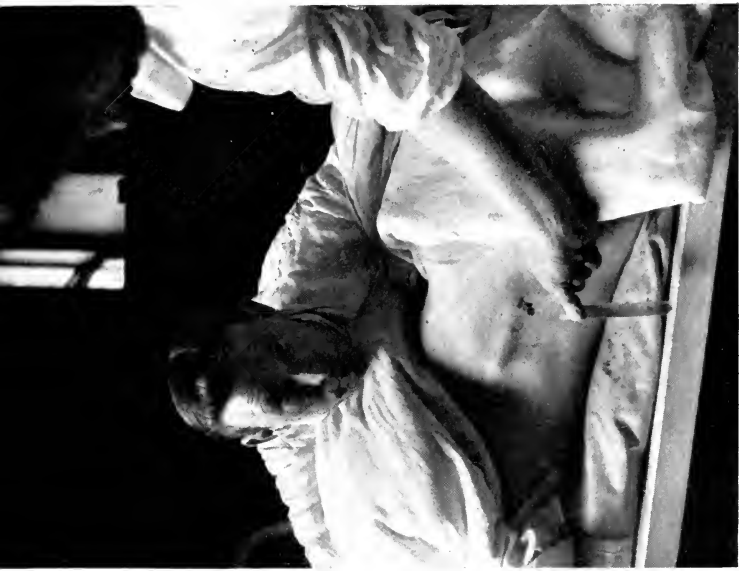
PLATE VII.

LUMBAR PUNCTURE.

A. Illustrating the position of patient and method of puncture (*vide* p. 410).
B. The subarachnoid space has been entered and the needle remains *in situ* while the cerebro-spinal fluid is allowed to escape into a graduated tube (*vide* p. 412).

Accidental Breakage of Needle.—This is a very rare occurrence and should never happen if the needle is of good quality and care is taken by the operator. Sophian, however, has observed the needle snap off in the middle after the canal has been reached, owing to a sudden contraction of the posterior spinal muscles. In some cases subsequently coming under his care extensive dissection failed to locate the broken end.

This author considers it best to wait and ascertain how much damage is done before radical measures are instituted; the dissection of the spinal membranes is an extremely delicate operation, and should not be performed unless absolutely indicated. In Sophian's experience, patients recovering from the meningitis have complained of no symptoms referable to the presence of the broken piece of needle.

Effect of Initial Lumbar Puncture.—The initial lumbar puncture in a case of cerebro-spinal fever is usually followed within 4-8 hours by a considerable fall in temperature, often to normal or subnormal (Fig. 49). This fall is quite independent of any anti-meningococcal serum administered at the first lumbar puncture, as it is often observed in cases to whom serum is not given; it is the result of the evacuation of the purulent exudate, and possibly to some extent of the relief of intracranial pressure. Within 6-12 hours, however, in the majority of cases, the temperature again rises.

Fig. 49.—Chart of an acute case on the second day of illness, illustrating the fall in temperature produced by the initial lumbar puncture.

Sequelae of Lumbar Puncture.—Cases of paraplegia have occasionally been reported as following lumbar puncture performed for the purpose of administrating a spinal anaesthetic; some of these have been ascribed to the actual needle puncture, but as the true cause this is doubtful. Isolated paralyses of the lower half of the

body have also been described, and the lesions attributed to injury of individual roots of the cauda equina. Such paralyses appear to affect almost exclusively the bladder, anus, or distribution of the external popliteal nerve. Owing to the relatively mesial position of the lowest sacral roots, it is easy to understand that they might be liable to injury during the performance of lumbar puncture, but in the opinion of most authors, when the intrathecal sac is entered at the usual sites, such sequelae are exceedingly rare. We have carefully examined over 120 patients recovered from cerebro-spinal fever for possible lesions of the cauda equina ; the number of punctures performed on each patient varied from four to thirty-five. In no case was any lesion discovered, there being not even the slightest trace of sensory change over the areas of distribution of the 4th and 5th sacral nerves. Consequently, any fear of untoward sequelae of repeated lumbar puncture may be safely dismissed.

The pain and weakness in the back, so often complained of for some considerable time after recovery from cerebro-spinal fever, is more probably a sequel of the disease itself than of repeated lumbar puncture. One of Foster and Gaskell's cases, who also suffered from well-marked auricular fibrillation, presented such alarming symptoms of collapse at the first lumbar puncture that it was considered, so long as appreciable progress was being made, no further puncture was advisable. The disease consequently ran a protracted course, the man not being free from symptoms for 40 days. During convalescence he exhibited the symptoms of pain and weakness in the back to a more marked degree than a patient who had received 12 or more punctures.

Administration of Serum

Dosage of Serum.—It was pointed out when dealing with the standardisation of anti-meningococcal serum that, in contrast to diphtheritic and tetanus antitoxin, there existed no definite measure of the efficiency of the serum ; consequently the dose is measured by volume. As a general rule, with certain exceptions that will be mentioned later, the amount of serum injected at a single administration should be at least 5 c.c. less than the quantity of cerebro-spinal fluid withdrawn. In our cases over 15 years of age the initial dose has varied from 30 to 45 c.c.; the usual dose is 30 c.c., but in very acute cases yielding a large amount of cerebro-spinal fluid, 40-45 c.c. may be given as an initial injection. The sub-

sequent sero-toxic reaction is certainly no more severe in cases receiving the larger doses than in many of those to whom 30 c.c. is administered ; in some, indeed, we found it less severe. As regards children, in relation to age, the following doses may be given :

1- 5 years	.	.	.	5-15 c.c.
5-10 „	.	.	.	10-20 c.c.
10-15 „	.	.	.	15-30 c.c.

Following the first injection, serum is continued daily in doses of 30 c.c. for adults and adolescents. The total amount of serum administered to an individual case is dealt with later (p. 422).

Method of Administration.—The serum is much better run in by the gravitation method, first introduced by Heiman in 1908, than injected by means of a syringe. However slowly the serum is forced in with a syringe, there is always a risk of respiratory failure occurring from a sudden increase of intracranial pressure. It has previously been shown (Chapter XI.) that the intrathecal administration of serum is accompanied by a fall in blood pressure. Often this fall is considerable ; in one acute case the blood pressure before and after the withdrawal of 50 c.c. of cerebro-spinal fluid was 118 mm., the evacuation of fluid having produced no change. Immediately after the administration of 30 c.c. of anti-meningo-coccal serum the blood pressure had fallen to 70 mm. Injection by means of a syringe tends to increase this fall in blood pressure with the consequent risk of respiratory failure and collapse. This we have seen occur, the patient only being brought round with difficulty.

In many hundreds of serum injections by means of the gravitation method we have never seen indications of collapse ; it seems unnecessary, therefore, if the respiration be carefully watched, to take the further precaution of registering the blood pressure as an ocular guide to injection by gravity.

The following is a description of the technique employed by us. The upper end of an indiarubber tube, about 18 inches long, is attached to a small glass funnel ; the lower end of the rubber tube is secured to a tubular piece of metal with a prolongation which fits into the spinal needle. About two or three inches above this, a small piece of glass tubing interrupts the continuity of the rubber tube to act as a " window," a metal clip being between this and the attachment fitting into the needle (Plate VIII.). Lumbar puncture having been performed and cerebro-spinal fluid evacuated

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(p. 412), the apparatus, previously sterilised by boiling, is taken and the tube and part of the funnel filled with sterile saline solution ; the clip is then released and the saline allowed to escape in order to displace the air, until its upper level reaches the tubular portion of the funnel.   Serum, warmed to body temperature, is then poured into the funnel, and the clip again released until the serum, known by its yellow colour, is seen at the " window."   Finally, the metal insertion is placed in the spinal needle and the serum allowed slowly to run in, the flow being regulated by alternately raising and lowering the funnel (Plate VIII.).   It is important to keep the spinal needle in the same position throughout the whole procedure to prevent displacement of its point from the spinal canal.

If the patient is straining, the inflow of serum may be very slow indeed and scarcely discernible ; he may also complain of considerable pain and " cramp " in the legs caused by the sudden rise of pressure acting on the roots of the cauda equina.   The site of pain most frequently indicated is down the back of the leg, and the hamstring muscles can occasionally be both seen and felt to twitch. Evidently this is due to stimulation by the inflowing serum of the upper roots of the great sciatic nerve on their way to the fourth and fifth sacral foramina.   To obviate the initial pain, the funnel should only be raised slowly from the horizontal level of the needle ; the pain also is less when the serum is warmed to body temperature than when it is injected cold.

In our earlier cases a complaint of cramp was almost invariable. We found, however, that by directing the patient, when his mental condition permitted, to breathe deeply with a somewhat long inspiration and short expiration, the inflow of the serum was greatly accelerated and he ceased to complain of cramp and pain.   On inspiration there is a considerable lowering of pressure in the intrathecal canal, with a corresponding increase during expiration. During the long inspiration, the serum flows rapidly, but when the expiration is long and the inspiration short, the serum scarcely moves.   This is easily observed by using a funnel with a long tubular lower end ; when the upper level of the serum is in the tube, the extremely rapid fall during inspiration can be watched, while the level remains almost stationary during expiration.   The great diminution of pain and cramp is due, no doubt, partly to the decreased pressure on the nerve-roots and partly to the fact that the patient's mind is more or less concentrated on the breathing.

A device employed by Sophian to diminish the pain and termed

PLATE VIII.

THE INTRATHECAL ADMINISTRATION OF SERUM.

(*Vide* p. 417.)

by him " water anaesthesia," consists in allowing the patient to suck water through a straw during the operation of lumbar puncture and serum injection.

When the injection of serum is completed, the needle is withdrawn and the small wound swabbed with an antiseptic. In our cases, equal parts of tincture and liniment of iodine are used, no dressing or collodion then being necessary. Finally, the foot of the bed is raised on blocks for about an hour to facilitate the upward flow of the serum. It has been shown by experiment, for example, by Carnegie Dickson, that methylene blue injected into the lumbar region of a fatal case of cerebro-spinal fever reaches the brain in a few minutes.

If any subsequent pain is complained of in the back or legs, 10-15 grains of acetyl-salicylic acid usually gives relief.

Some observers (e.g. Dopter) recommend washing out the subarachnoid space with normal saline before injecting the serum ; we have not found this proceeding of any material benefit (vide p. 453).

Accidents during Serum Injection.—Accidents during the intrathecal administration of serum are relatively infrequent ; by injecting anti-meningococcal serum slowly by means of the gravitation method, in many hundreds of administrations we have met with no untoward result. In our experience, the same statement applies to the intrathecal injection of antitetanic, mercurialised, and " salvarsanised " serum.

Such disturbances as have been described are due to a sudden increase of intracranial pressure with a consequent fall in blood pressure and depression of the respiratory centre. Carter, on dogs, and Sophian, in the human subject, found that such changes occurring during the intraspinal injection of fluid were entirely or for the greater part dependent upon mechanical causes, being influenced especially by the quantity of fluid injected, the pressure used, and the rate of injection. Carter showed that the symptoms could be relieved almost immediately by cocaine given intramuscularly or intravenously. The first abnormal sign is usually some embarrassment of respiration, the breathing becoming shallow and slow and occasionally irregular. If the serum be forced in with a syringe, the breathing may stop suddenly, although the heart continues to act well. At other times, such symptoms result from the too rapid administration or the injection of too large a quantity of serum. Should symptoms of respiratory embarrassment occur,

the injection must at once be stopped by lowering the funnel and allowing what serum that has already entered the subarachnoid space to escape. Artificial respiration and the injection of cocaine and atropine in full doses will usually suffice to restore the patient.

Using the gravitation method, allowing the serum to enter the intrathecal sac only very slowly, the flow being regulated by alternately raising and lowering the funnel, and watching carefully the patient's respiration, we have not met with any indications of collapse ; consequently, with care, it is not considered necessary, as advocated by Sophian, to register the blood pressure throughout the operation.

Occasionally, incontinence of faeces may occur during the inflow of serum. This is no doubt due, as with lumbar puncture, to the stimulation of the third and fourth sacral nerves. Care, however, should be taken to ascertain that it is not due to collapse.

Continuance of Serum Administration.—Following the initial dose, serum injection is repeated daily, usually in doses of 30 c.c., after as much cerebro-spinal fluid as possible has been evacuated. In acute cases, the second dose may be given twelve hours after the first. Generally, our cases have been received during the afternoon or evening ; lumbar puncture has been performed and serum injected at once. On the following morning the procedure has been repeated and continued daily until clinical improvement, as indicated by a normal mental and sphincter condition, decreased muscular rigidity, absence of meningococci from the cerebro-spinal fluid, etc., is quite definite and decided. After the second injection there is seldom any distinct advantage in repeating the dose of serum every twelve hours ; if, however, owing to only a small amount of cerebro-spinal fluid being obtainable, the full dose of serum cannot be given at the morning lumbar puncture, a further injection may be given during the evening.

However great the improvement may appear, serum should be given on at least four successive days, and on no account should it be withdrawn if meningococci are still visible in stained films of the cerebro-spinal fluid or obtainable on culture. As a rule, organisms are not found on the few days before really definite improvement takes place. The persistence of meningococci in the cerebro-spinal fluid demands the continuation of daily serum injections until the organisms have disappeared, as until this result is achieved there is no certainty that the patient is free from danger.

Should signs of a recrudescence of meningitis appear after the period of serum administration has ceased, the injection of serum must be at once resumed and repeated daily until further improvement occurs, lumbar puncture then being continued until a clear fluid is obtained. Owing to the risk of anaphylaxis, serum administration should not be resumed without first inducing anti-anaphylaxis if the period since the last injection exceeds 8-10 days (*vide* p. 470) ; it is of considerable importance, however, to overcome the infection, as far as possible, in one continuous course of serum treatment.

The Amount of Serum injected in Relation to the Amount of Cerebro-spinal Fluid withdrawn.—As a general rule the amount of cerebro-spinal fluid evacuated by lumbar puncture should exceed by at least 5 c.c. the quantity of serum injected. In certain cases in which the amount of cerebro-spinal fluid obtainable is less than that of the serum it is desired to administer, an exception may be made. Provided that there is no evidence of increased intracranial pressure and that the serum is not forced in with a syringe, but merely allowed to flow in at not more than 12-18 inches water pressure by the gravitation method, we have found the proceeding quite safe ; as a precaution, however, the patient's respiration should be carefully watched. In such instances the amount of serum given may equal or even exceed that of the cerebro-spinal fluid withdrawn. At the pressure mentioned and by the gravitation method, the serum usually will cease to flow when the intrathecal pressure is approaching the limits of safety. Examples are as follows :

(1) Acute case recovering after a 14 days' course :

    5th day : lumbar puncture = 15 c.c. of blood-stained fluid under practically no pressure. 30 c.c. of serum run in easily, no change occurring in the patient's respiration.

    4th day : lumbar puncture = 15 c.c. turbid fluid, slightly blood-stained — no pressure, 15 c.c. run in at 18 inches water pressure ; no further quantity would enter.

(2) Acute case recovering after 12 days' course :

    5th day : 28 c.c. turbid fluid, no pressure. 30 c.c. of serum run in easily.

Similar results were observed on several occasions with other patients recovering.

When there is distinct evidence of increased intracranial pressure, *e.g.* symptoms of internal hydrocephalus, the injection of a larger amount of serum than of cerebro-spinal fluid withdrawn must not be entertained.

Total Amount of Serum administered to an Individual Case.— In our series of cases the total amount of anti-meningococcal serum administered to an individual patient has varied in different cases from 120 c.c. to 600 c.c. According to Netter, a total dosage up to 800 c.c. may be given without ill effect. In a series of 46 consecutive adult cases which recovered, excluding those of an abortive type, in 15 cases four 30 c.c. doses of serum only were necessary ; of these 15, 6 were very acute cases and unconscious or profoundly delirious when admitted to the ward on the first or second day of illness ; of the remaining 9 patients 4 were delirious, incoherent, and exhibited incontinence or retention of urine. The total amount of serum given in the 15 cases varied from 120 to 135 c.c. per patient. 13 cases (8 severe and 5 moderate) received five doses of serum on successive days, the total amounts varying between 127 and 150 c.c.

In the remaining 18 of the 46 cases the individual doses and the total amounts of serum were as follows :

Acute Cases.

1. Acute case recovering after 9 days' course : 7 doses of serum.
                                                 (Dose 30 c.c.) Total amt. 210 c.c.
2.   ,,   ,,   ,,   13 days' course : 8 doses of serum.
                                                 (Dose 30 c.c.) Total amt. 240 c.c.
3.   ,,   ,,   ,,   14 days' course : 8 doses of serum.
                                                 (Doses 30-40 c.c.) Total amt. 250 c.c.
4.   ,,   ,,   ,,   14 days' course : 9 doses of serum.
                                                 (Doses 18-30 c.c.) Total amt. 195 c.c.

Acute Cases becoming Subacute.

5. Acute case recovering after 23 days' course : 9 doses of serum.
                                                 (Doses 25-30 c.c.) Total amt. 265 c.c.
6.   ,,   ,,   ,,   24 days' course : 11 doses of serum.
                                                 (Doses 12-30 c.c.) Total amt. 307 c.c.
7.   ,,   ,,   ,,   28 days' course : 8 doses of serum.
                                                 (Dose 30 c.c.)   Total amt. 240 c.c.
8.   ,,   ,,   ,,   40 days' course : 17 doses of serum.
                                                 (Doses 10-30 c.c.) Total amt. 420 c.c.

Recrudescent Cases (originally Acute).

9. Case recovering after 11 days' course : 5 doses of serum.
                               (Dose 30 c.c.)   Total amt. 150 c.c.
10.   ,,   ,,   15 days' course : 8 doses of serum.
                               (Dose 30 c.c.)   Total amt. 240 c.c.
11.   ,,   ,,   17 days' course : 9 doses of serum.
                               (Dose 30 c.c.)   Total amt. 270 c.c.
12.   ,,   ,,   19 days' course : 8 doses of serum.
                               (Dose 30 c.c.)   Total amt. 240 c.c.
13.   ,,   ,,   22 days' course : 8 doses of serum.
                               (Doses 20-30 c.c.)   Total amt. 230 c.c.
14.   ,,   ,,   24 days' course : 10 doses of serum.
                               (Doses 30-45 c.c.)   Total amt. 315 c.c.
15.   ,,   ,,   80 days' course : 15 doses of serum.
                               (Dose 20-30 c.c.)   Total amt. 460 c.c.

(Cases 9 and 10 came under treatment only when the recrudescence occurred.)

Subacute Cases.

16. Mild case recovering after 8 days' course : 4 doses of serum.
    (Dose 30 c.c.)   Total amt. 120 c.c.
17. Moderately severe case recovering after 17 days' course :
    6 doses of serum.   (Dose 30 c.c.)   Total amt. 180 c.c.
18. Moderately severe case recovering after 30 days' course :
    8 doses of serum.   (Doses 12-30 c.c.)   Total amt. 222 c.c.

Effects of Serum Administration

Effect on the Appearance and Cytological Characters of the Cerebro-spinal Fluid.—One of the results of the initial dose of anti-meningococcal serum is the stimulation of leucocytosis. Consequently, in a subacute case yielding a cerebro-spinal fluid only very slightly turbid at the first lumbar puncture, the fluid obtained on the day following will often appear more turbid, although the clinical symptoms may have improved. The intrathecal injection of most sera produces such a leucocytosis, e.g. in tetanus the first cerebro-spinal fluid withdrawn is quite clear ; after the intra-spinal injection of tetanus antitoxin, however, the fluid obtained on the following day is distinctly turbid, and exhibits a well-marked polymorphonuclear leucocytosis.

In cases of cerebro-spinal fever progressing favourably, the turbidity of the cerebro-spinal fluid gradually diminishes with each successive injection, the protein content decreasing progressively from day to day. Also the polymorphonuclear cells become less and less degenerate and, after the first week or so, gradually diminish

TABLE XXII

EFFECT OF ANTI-MENINGOCOCCAL SERUM UPON MENINGOCOCCI IN THE CEREBRO-SPINAL FLUID IN DIFFERENT CLINICAL TYPES OF CEREBRO-SPINAL FEVER

(d.e. = direct examination; c. = culture; + = meningococci present; - = meningococci absent)

	Day of Disease on which Treatment was begun	1st Examination d.e.	1st Examination c.	Amount of Serum given between 1st and 2nd Examinations	2nd Examination d.e.	2nd Examination c.	Amount of Serum given between 2nd and 3rd Examinations	3rd Examination d.e.	3rd Examination c.	Amount of Serum given between 3rd and 4th Examinations	4th Examination d.e.	4th Examination c.
A. CASES RECOVERING—												
(1) Acute cases recovering after a short course:												
Case 1	1st	+	+	30 c.c.	-	-	60 c.c.	-	-	...	·	·
,, 2	1st (late)	+	+	45 c.c.	-	-	60 c.c.	-	-	30 c.c.	-	-
,, 3	1st (,,)	+	-	60 c.c.	-	-	30 c.c.	-	-	...	·	·
,, 4	1st (,,)	+	-	50 c.c.	+	-	25 c.c.	-	-	30 c.c.	-	-
,, 5	2nd	+	+	60 c.c.	-	-	50 c.c.	-	-	...	·	·
,, 6	2nd	+	+	30 c.c.	+	-	60 c.c.	-	-	...	·	·
,, 7	2nd	+	-	120 c.c.	+	-	30 c.c.	+	-	30 c.c.	-	-
,, 8	2nd	+	-	30 c.c.	+	-	30 c.c.	-	-	30 c.c.	-	-
,, 9	3rd	+	+	40 c.c.	-	-	30 c.c.	-	-	...	·	·
,, 10	3rd	+	+	60 c.c.	+	-	60 c.c.	-	-	30 c.c.	-	-
,, 11	3rd	+	-	60 c.c.	+	-	60 c.c.	-	-	...	·	·
,, 12	4th	+	+	100 c.c.	+	+	30 c.c.	+	-	30 c.c.	-	-
(2) Acute cases becoming sub-acute:												
Case 13	2nd	+	+	45 c.c.	+	+	45 c.c.	+	-	120 c.c.	-	-
,, 14	2nd	+	+	85 c.c.	+	+	80 c.c.	+	-	140 c.c.	-	-
,, 15	3rd	+	+	90 c.c.	+	+	30 c.c.	+	-	60 c.c.	-	-
(3) Subacute cases—moderately severe:												
Case 16	1st (clear fluid)	-	-	Nil	+	+	30 c.c.	+	-	90 c.c.	-	-
,, 17	2nd	+	-	60 c.c.	-	-	30 c.c.	-	-	...	·	·
,, 18	2nd	+	-	30 c.c.	-	-	30 c.c.	-	-	...	·	·

Case		Day			Dose			Dose			Note		
„	19	3rd	+	+	30 c.c.	+	+	30 c.c.		−	−	…	·	·
„	20	3rd	+	+	30 c.c.	+	−	60 c.c.		−	−	…	·	·
„	21	3rd	+	+	60 c.c.	+	−	60 c.c.		−	−	…	·	·
„	22	3rd	+	+	60 c.c.	+	+	60 c.c.	+	+	+	30 c.c.		
„	23	3rd	−	+	60 c.c.	−	−	60 c.c.		−	−	…	·	·
„	24	3rd	−	−	30 c.c.	+	−	30 c.c.		−	−	…	·	·
„	25	3rd	+	−	60 c.c.	−	−	60 c.c.	+	+	+	60 c.c.		
„	26	3rd	−	+	30 c.c.	+	−	30 c.c.		−	−	…	·	·
„	27	4th	+	+	30 c.c.	+	+	30 c.c.		−	−	…	·	·
„	28	4th	+	+	30 c.c.	−	−	30 c.c.		−	−	…	·	·
(4) Subacute cases—mild:														
Case	29	2nd	+	+	30 c.c.	−	−	30 c.c.		−	−	…	·	·
„	30	3rd	−	+	30 c.c.	+	−	60 c.c.		−	−	…	·	·
„	31	3rd	−	−	60 c.c.	−	−	60 c.c.		−	−	…	·	·
„	32	4th	+	+	30 c.c.	+	+	60 c.c.		+	+	…	·	·
„	33	5th	+	+	30 c.c.	+	+	60 c.c.		−	−	…	·	·
B. Cases proving Fatal—														
(1) Acute fatal type:														
Case	34	2nd	+	+	30 c.c.	+	+	30 c.c.	Died 4th day	−	−	30 c.c.	−	+
„	35	2nd	+	+	70 c.c.	+	+	30 c.c.	„ 5th „	+	+	60 c.c.	−	+
„	36	2nd	+	+	60 c.c.	+	+	60 c.c.	„ 6th „	+	+	30 c.c.	−	+
„	37	2nd	+	+	30 c.c.	+	+	60 c.c.	„ 5th „	+	+	30 c.c.	+	+
„	38	3rd	+	+	60 c.c.	+	+	30 c.c.	„ 6th „	+	+	30 c.c.	−	−
„	39	4th	+	+	60 c.c.	+	+	60 c.c.	„ 6th „	+	+	30 c.c.	·	·
(2) Acute Case—long course:														
Case	40	2nd	+	+	60 c.c.	+̣		…	Died 31st day (meningococci present throughout)	+	+	60 c.c.	+	+
(3) Progressively purulent type:														
Case	41	2nd	+	+	30 c.c.	+	+	45 c.c.	25 c.c.	+	+	+	+	−
„	42	3rd	+	+	60 c.c.	+	+	90 c.c.	…	−	−		·	·
„	43	3rd	+	+	30 c.c.	+	+	30 c.c.	10 c.c.	+	+	+	−	+
„	44	3rd	+	+	60 c.c.	+	+	70 c.c.	10 c.c.	+	+	+	−	+
„	45	3rd	+	+	60 c.c.	+	+	30 c.c.	…	+	+	+	−	+
„	46	4th	+	−	30 c.c.	−	−	30 c.c.	…	−	−		·	·

It will be noticed that even in fatal types the viability of the organism is in many cases diminished, as shown by the lack of power to reproduce on artificial culture media.

in number. With this diminution there occurs a relative increase in the mononuclear cells until, in the final stages, the polymorpho-nuclear cells disappear and the mononuclear cells are found in no more than their normal number.

Effect upon the Meningococci.—In most cases, extracellular organisms rapidly diminish in number until the greater portion are seen intracellularly. This is followed by a gradual disappearance of all meningococci from stained films of the centrifugalised deposit ; as a rule, immediately prior to the disappearance of organisms their viability decreases, as shown by failure to grow in culture although visible on direct examination. The effect of serum administration on the meningococci present in the cerebro-spinal fluid in relation to the clinical type of case is shown in Table XXII. (a series of 46 consecutive cases) on pp. 424, 425.

Effect of Serum Treatment on the Course of Disease.—Occasion-ally following the initial injection there occurs a further rise in temperature and a temporary aggravation of the meningitic symptoms. According to Levy, this result is due to the rapid liberation of endotoxin resulting from the bacteriolytic action of the serum.

Prior to the employment of anti-meningococcal serum, cerebro-spinal fever was a disease either rapidly fatal or of long duration frequently terminating in death. In 350 cases occurring during the New York epidemic of 1905–6, before the introduction of serum treatment, Holt showed that the disease lasted one week in less than 3 per cent of those cases recovering, and five weeks or longer in 50 per cent of all cases. With these figures may be contrasted those of Flexner and Jobling, who found that the average duration of *active symptoms* in 288 serum-treated cases was 11 days.

Of our series of cases treated by serum, continued lumbar puncture and vaccine, the average duration of the *total course,* as estimated from the day of onset until a clear cerebro-spinal fluid was obtained on lumbar puncture, was 14 days.

Effect of Serum in preventing Complications.—In addition to the reduction in mortality, one of the greatest benefits of serum treatment is the prevention of the serious complications of the disease. Although varying greatly in different epidemics, it was estimated that prior to the introduction of serum treatment, com-plications occurred in approximately 20–25 per cent of cases. Netter, before the employment of serum, found permanent ill

effects of the disease in 23·5 per cent. Since the adoption of serum treatment this author has observed such sequelae in only 6·3 per cent. In 295 recovered cases Flexner reports only 3·4 per cent of the more severe sequelae. Deafness remains the least affected, but imbecility and extensive paralyses are now very rare (*vide* Chapter XX.).

Repeated Lumbar Puncture

When clinical improvement is quite decided and organisms have disappeared from the cerebro-spinal fluid, our practice is to discontinue the administration of serum ; lumbar puncture, however, is still performed daily until a cerebro-spinal fluid quite clear to the naked eye is obtained, pyrexia being absent and the patient being free from any symptoms suggesting hydrocephalus. In fact, the only sign usually present at this stage is some degree of muscular rigidity, as shown by slight stiffness of the neck and spine and a modified Kernig's sign ; the latter is usually the last symptom to disappear. For all practical purposes, however, when the cerebro-spinal fluid is clear, sterile, and the pressure normal, no evidence of hydrocephalus being present, and pyrexia and subjective symptoms have disappeared, the course may be said to have ended. Following the cessation of serum administration, the number of days of repeated lumbar puncture in our cases has varied from 3 to 14. There is no doubt that in addition to shortening the course, the repeated draining of the intrathecal sac tends to inhibit the development of any serious degree of hydrocephalus.

Of 66 cases treated by the method described, 52 recovered (*vide* p. 396). Of the 14 proving fatal, in no case was death due to internal hydrocephalus : 13 cases were either of the fulminating, acute fatal, or progressively purulent type ; the remaining case was not received by us until the third day of a recrudescence (36th day of total illness), the early part of the patient's illness not being recognised as subacute cerebro-spinal fever. The case proved fatal on the 43rd day of the disease from generalised hydrocephalus due to a blockage by fibro-purulent exudate having occurred in the region of the foramen magnum. Of the 52 cases recovering, only four showed temporary symptoms of generalised hydrocephalus subsequent to the first week, and one those of internal hydrocephalus.

By varying the site of puncture from time to time, we have never experienced any trouble with the skin wounds. We find

that the skin can be kept in a relatively better condition by avoiding collodion dressings, etc. ; on withdrawal of the needle after each operation is completed, the wound is merely swabbed with a mixture of equal parts of tincture and liniment of iodine.

The procedure to be adopted, should symptoms suggestive of hydrocephalus occur, is described under the treatment of this complication (*vide* p. 448).

Vaccine Treatment

During 1915 vaccines were frequently employed concurrently with other methods of treatment. The few cases referred to by Rolleston as receiving vaccine treatment, many of which one of us had the opportunity of observing, gave an apparent mortality of only 25 per cent. Most of these cases, however, were well on the way to recovery before the vaccine was given ; they were also treated with either anti-meningococcal serum or soamin in addition to lumbar puncture. Of other observers, Warren Crowe considered that autogenous vaccines did good in influencing temperature. He began with the very small dose of one million organisms, while Walker Hall gave a polyvalent vaccine every two days in gradually increasing doses from 25 to 500 millions, preferring it to serum. J. R. Collins recommended starting with a half to one million organisms, and was of the opinion that it did good especially in chronic cases. Horder mentions a patient of Garrod's, a child aged seven years, whom autogenous vaccine certainly appeared to benefit, the case running rather a prolonged course and threatening to develop chronic hydrocephalus. Sophian believed that in many chronic and subacute cases vaccines were more efficacious than serum. Fairley and Stewart used vaccines in subacute and chronic cases ; they state that it is not uncommon to see a case that has been running an irregular pyrexia for three weeks enter on convalescence shortly after the exhibition of vaccine. Colebrook considers that vaccines assist the patient's own anti-bacterial defences in dealing with the meningococcus, while the serum checks multiplication in the cerebro-spinal fluid and promotes phagocytosis. Flack also mentions cases only slowly improving in which vaccines were of value.

The experiences of 1915 left us with the distinct impression that vaccines were of material assistance once cases had passed the initial acute stage, and were full worthy of another trial.

F. E. Taylor, having failed to demonstrate agglutinins in the

cerebro-spinal fluid of rabbits immunised against the meningo-coccus, considers that the weight of evidence goes to prove that bacterial antibodies do not pass over from the blood to the cerebro-spinal fluid, and that therefore little benefit can be expected to result from the subcutaneous administration of vaccines in cerebro-spinal fever. It would seem, however, too great a general assumption to draw that because no agglutinating properties are discoverable in the cerebro-spinal fluid of injected rabbits, no antibodies whatever are present. In our experience we have seldom found any marked degree of agglutinating power present in the blood of cerebro-spinal fever patients, even against their own organism, either during or immediately after the course of the disease; nevertheless, recovery must to some extent have occurred owing to the development of antibodies of some description. Until more definite information is available concerning not only the action of anti-meningococcal serum but also the nature of the antibodies on which relative immunity from cerebro-spinal fever depends, we do not consider it justifiable to discard the results of clinical experience and jettison vaccine treatment entirely.

Dosage of Vaccine.—We have administered vaccine in somewhat larger doses than are usually employed. Thus, in adults and adolescents a dose of 250 million organisms is injected subcutaneously at some time during the first three days of illness, the second dose consisting of 500 millions, and each of the subsequent doses being increased by 500 millions up to a maximum of 2500 millions. The last two doses are not always necessary. In children the initial dose may be 10 millions, the second 50 millions, and each subsequent dose increased by 100 millions. The vaccine is preferably autogenous, but as this takes some time to prepare, a polyvalent vaccine is given at first and is replaced by the autogenous as soon as the latter is available. The polyvalent vaccine we have used consists of the four types of meningococci differentiated by Gordon.

If the reaction to a particular dose is at all pronounced, the same dose is repeated four days later; usually no reaction follows this repetition. The increase of 500 millions is then made on the next occasion of administration. When meningococci are not cultivated from the patient's cerebro-spinal fluid, polyvalent vaccine is used throughout.

Results of Vaccine Treatment.—Cases in which the effect of vaccine is certainly beneficial are those subacute cases which tend

to run a somewhat long course. Of our own series the following may be mentioned :

In one case, originally acute, no cerebro-spinal fluid could be obtained on or after the 30th day of illness in spite of lumbar puncture being performed in several interspaces as high as that between the 1st lumbar and 12th thoracic vertebrae ; on the previous day 35 c.c. of fluid had been withdrawn in this latter situation after failure to obtain any from the interspaces below. Following the usual initial dose of 250 millions, the patient had been given 500 millions on the 6th day ; on the morning of the 7th day the temperature reached normal for the first time, falling from an average of 101·5° F. It rose, however, on the following morning, and a dose of 1000 millions produced no apparent change. Serum administration was discontinued after the 16th day. Following a dose of 2000 million organisms on the 18th day, the evening temperature rose to 103° F.—the highest point for four days, but fell to 99° next morning and remained low for two days with some improvement in the patient's condition. According to our usual custom, when an apparent reaction occurred, however, the same dose (2000 millions) was repeated on the 22nd day ; on the 24th day the temperature fell from 102° to 99°. A further dose of 200 million organisms was given on the 26th day, and resulted in a fall from 99·8° to 98·2° ; the same dose repeated on the 31st day produced no apparent change. Since the 29th day no cerebro-spinal fluid had been obtainable and the patient had become drowsy, incoherent, tremulous, incontinent, and emaciated ; in fact, all signs of internal hydrocephalus were present, including vomiting. On the 35th day the temperature at 2 P.M. had risen to 102° ; at 6 P.M. another dose of 2000 million organisms was injected. On the following morning the temperature fell to normal, rising only to 99° that evening. Two days later the patient's mental condition appeared better, and vomiting, previously quite frequent, had ceased. By the 39th day he had improved considerably, his mind was clear, and neck rigidity considerably less. On the 40th day 2500 million organisms were given ; the temperature rose only to 99° and was followed by further improvement. The same dose was repeated on the 44th day without any rise of temperature. Incontinence of urine, the symptom to remain longest, finally disappeared on the 45th day (Fig. 50).

In another case, that of a man aged 25, the subacute course continued for 46 days ; after the first few days the patient's mental

condition was practically normal. Although general improvement was definite, the pyrexia persisted with slight morning remissions. The cerebro-spinal fluid also remained turbid although no organisms could be seen on direct examination or cultivated. In spite of frequent lumbar puncture this state continued, the temperature varying between normal and 102·6° F., until a dose of 2000 million organisms was reached (31st day). Following this, the temperature did not rise above 100°; after 2500 millions, given four days later, the temperature fell to normal and remained at this level, excepting
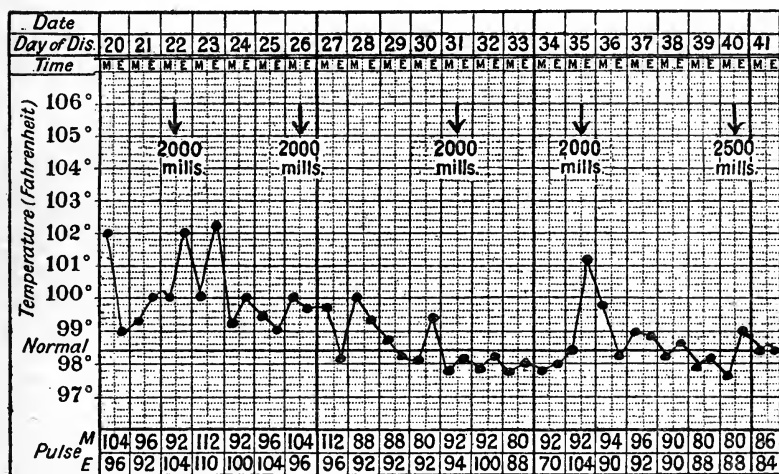
Fig. 50.—Vaccine Treatment.   Chart of a case originally acute but becoming subacute and tending to run a protracted course.   (*Vide* p. 430.)

for a slight evening rise two days later. The cerebro-spinal fluid was quite clear within a week.

Of other cases in which vaccine appeared to play no small part in bringing about recovery the following may be mentioned:

A recrudescent case, aged 15, running a course of 80 days (Case XXII.); two subacute cases not received until the 9th and 14th days of illness respectively—recovery occurred after 10 and 14 days in each case; two acute cases becoming subacute and recovering after illnesses lasting 23 and 24 days respectively; also Cases LXII. and LXIII. (p. 436).

No ill effects attributable to the vaccine were ever observed. In some cases the third or fourth dose was followed by a transient rise of temperature; subsequent increased doses, however, failed to produce any appreciable change in temperature or pulse rate.

In patients exhibiting a rise of 2°-3° F. following the injection of vaccine, repetition of the dose usually produced no apparent reaction, and the usual increase given later was not followed by any marked rise of temperature. In a subacute case not received until the 14th day of illness, the second dose of vaccine, given on the 18th day of illness, was followed by a rise in temperature from 98·2° to 102·2°; pyrexia, however, was absent after eight hours, and did not recur after repetition of the same dose (500 millions) given on the 22nd day. The patient recovered on the 28th day of illness—14 days after commencement of treatment.

A slight local reaction occurred in two or three cases with a dose of 1500 millions, but 2000 millions given four days later failed to produce a similar result.

Treatment in Relation to Clinical Type of Case

Acute Types.—Many cases, although at first extremely acute and severe, are characterised by their ready and comparatively rapid response to treatment. Thirteen acute cases recovering after a short course, with the treatment given, are shown in the following table:

TABLE XXIII

TREATMENT IN ACUTE CASES RECOVERING AFTER A SHORT COURSE

Case.	Day of Disease on which Treatment was begun.	No. of Doses of Serum.	Individual Doses in c.c. and Days on which given.								Total Dosage (c.c.).	No. of Days Lumbar Puncture was repeated following stoppage of Serum.	Vaccine.	Total Course (Days).
			1	2	3	4	5	6	7	8				
													Mill.	
1	2nd	4	—	30	30	30	20	.	.	.	110	3	250–1000	8
2	2nd	4	—	30	30	30	30	.	.	.	120	5	250–1500	10
3	3rd	4	—	—	40	30	30	30	.	.	160	4	250–1000	10
4		4	—	45	30	30	30	.	.	.	135	5	250–1500	10
5	1st (late)	4	45	30	30	30	.	.	.	.	135	3	250–1500	7
6	1st (,,)	5	30	30	30	30	30	.	.	.	150	3	250–1000	8
7	2nd	5	.	30	30	30	30	30	.	.	150	3	250–1000	9
8	3rd	5	—	30	30	30	30	30	30	30	150	3	250–1000	10
9	1st	6	* { 30 / 30 }	30	30	30	20	.	.	.	170	1	250–1000	6
10	3rd	7	—	—	—	30	30 { 30	30	30		220	4	250–2000	14
11	2nd	7	{ 30 / 30 }	{ 30 / 30 }	30	30	30	.	.	.	210	3	250–1500	9
12	3rd	8	—	—	30	30	{ 30 / 30 }	30	30	30†	240	4	250–1500	13
13	1st (late)	9	40	{ 10 / 15 }	30	{ 12 / 18 }	20	30	30	.	195	7	250–2500	14

* 30 c.c. intramuscularly, cerebro-spinal fluid being clear (pre-meningitic stage).
† 30 c.c. also given 9th day. The last day of the course was that on which a clear cerebro-spinal fluid was obtained on lumbar puncture.

Cases 11 and 13 were extremely severe; the former was admitted comatose on

the fourth day of illness. In the latter, response to serum treatment was slow, no doubt owing to the fact that the full dose of serum would not always flow in ; by the 11th day, however, improvement was considerable. Case 9 (Case II. p. 63) was admitted with a purpuric rash but with no signs of meningitis, the cerebro-spinal fluid being perfectly clear ; he was given 30 c.c. of anti-meningococcal serum intramuscularly. Within eight hours, turbid fluid was obtained on lumbar puncture and serum given intrathecally.

Case XVII. (p. 150) illustrates an acute case recovering after a short course.

Acute Cases which become Subacute.—Acute cases may respond to treatment as regards improvement, but instead of recovering after a comparatively short course, pass into a subacute stage. Serum treatment overcomes the more acute symptoms, but after the first ten or twelve days appears to exert less effect. Symptoms of hydrocephalus may develop in spite of repeated daily lumbar puncture ; if this latter operation is persisted in, however, provided fluid is obtained, the case usually recovers. Vaccine treatment is of considerable assistance (*vide*, p. 429).

Of our series, two such cases (severe) may be mentioned as illustrations :

(1) The patient, aged 24 and admitted on the 3rd day of illness, received a total of 260 c.c. of serum during the first 12 days ; vaccine was given as usual. Serum was also given on the 15th and 17th days, the case showing a tendency to become hydrocephalic from the 14th to the 17th days. Lumbar puncture was continued for 11 days following the cessation of serum administration. Distinct improvement was seen following the doses of vaccine (1000 and 1500 millions) given on the 17th and 21st days. On the 24th day clear cerebro-spinal fluid was obtained.

(2) The patient was admitted acutely ill on the 2nd day of illness with some purpuric spots present over the lower portion of the trunk. On each of the first nine days in hospital, he received 30 c.c. of serum per day with slight improvement ; from the 10th to the 18th day lumbar puncture was performed daily ; four doses of serum were given during this period. Following this, only small quantities of cerebro-spinal fluid were obtainable, and the patient developed symptoms of hydrocephalus. From this point onwards the case has been commented upon when dealing with vaccine treatment (p. 430). He eventually recovered on about the 40th day, the ultimate result appearing largely due to vaccine therapy.

Acute Cases running a Long Course.—Acute cases may occur which, instead of recovering or becoming subacute, remain acutely

ill for three or four weeks until death ensues. Such cases, however, are uncommon ; at the outset they exhibit marked delirium and incontinence, and a purpuric rash is not infrequently present. The probability is that they would prove fatal much more rapidly but for the modifying effect of treatment. Case VI. (p. 84) is an example ; the patient was admitted on the 12th day of illness, the cerebro-spinal fluid being crowded with meningococci. He received a total of 480 c.c. of serum in 30 c.c. doses, but death occurred on the 31st day.

In a second case, aged five years and proving fatal on the 21st day, serum was given daily until death without any appreciable effect. The case, however, occurred early in 1915 when the serum available was not of a high standard.

Acute Fatal Type.—It was pointed out when dealing with the course in this type of case (p. 141) that the progress is uniformly downwards, treatment being without apparent effect. All cases met with received at least 30 c.c. of serum per day ; in some cases the initial dose was 45 c.c., and in several, doses were given twice daily.

Subacute Types.—*Mild Subacute Cases.*—Subacute cases of a mild nature respond very quickly to treatment. The following table illustrates the treatment in four such cases :

TABLE XXIV

MILD SUBACUTE CASES

Case.	Day of Disease on which Treatment was begun.	No. of Doses of Serum.	Individual Doses in c.c. and Days on which given.								Total Dosage (c.c.).	No. of Days Lumbar Puncture was repeated following stoppage of Serum.	Total Course (Days.)
			1	2	3	4	5	6	7	8			
1	2nd	4	–	30	30	30	20	.	.	.	110	2	7
2	3rd	4	–	–	30	30	15	30	.	.	105	2	8
3	4th	4	–	–	–	30	30	30	30	.	120	1	8
4	5th	2	–	–	–	30	30	30	30	.	120	2	9

When the first sample of cerebro-spinal fluid obtained is only very slightly turbid, the first dose or two of serum often produces increased leucocytosis in the cerebro-spinal fluid, resulting in an increased turbidity. Similarly, in cases of tetanus and acute anterior poliomyelitis, the intrathecal injection of serum is frequently

followed by meningeal symptoms of a mild nature, and the cerebro-spinal fluid, clear at the first withdrawal, will be found slightly turbid, exhibiting a cell count of about 10,000 per c.mm.

Moderately Severe Subacute Cases.—In many subacute cases, although severe, the response to treatment is fairly rapid ; in such instances more than five doses of serum are seldom required. Owing to their subacute nature, some of the cases escape recognition until the disease has been present for some days ; patients not received until the 4th day of illness or later would probably have been only mild cases had it been possible to begin treatment earlier.

The following table summarises the treatment in 11 moderately severe subacute cases recovering within 14 days :

TABLE XXV

MODERATELY SEVERE SUBACUTE CASES RECOVERING WITHIN 14 DAYS

Case.	Day of Disease on which Treatment was begun.	No. of Doses of Serum.	Individual Doses in c.c. and Days on which given.								Total Dosage (c.c.)	No. of Days Lumbar Puncture was repeated following stoppage of Serum.	Vaccine. Mill.	Total Course (Days).
			2	3	4	5	6	7	8	9				
1	2nd	4	30	30	30	30	.	.	.	.	120	2	250–1000	7
2	3rd	4	–	30	30	30	30	.	.	.	120	8	250–1500	14
3	4th	4	–	–	35	15	30	30	.	.	90	2	250–1000	9
4	4th	5	–	–	30	30	20	25	25	.	130	5	250–1500	13
5	2nd	5	30	30	30	30	30	.	.	.	150	6	250–1500 "	12
6	2nd	5	15	{ 30 20	30	25	.	.	.	.	120	3	250–1000	8
7	3rd	5	–	30	30	25	30	12	.	.	127	5	250–1500	12
8	3rd	5	–	30	20	30	30	30	.	.	140	3	250–1000	10
9	3rd	5	–	30	30	30	30	30	.	.	150	3	250–1500 "	10
10	3rd	5	–	30	30	30	30	30	.	.	150	5	250–1500	12
11	6th	4	–	–	–	–	30	30	30	30	120	3	250–1000	12

Subacute cases not received until relatively late in the disease, the institution of specific treatment thereby being delayed, tend to run a longer course. The following three cases may be mentioned as illustrating the treatment.

(1) CASE LXI.—The patient, aged 18, was regarded in a local auxiliary hospital as a case of influenza, and, therefore, was not received by us until the 10th day of illness. Five doses of serum (each 30 c.c.) and three subsequent lumbar punctures, however, sufficed to bring about recovery (total course—17 days) ; vaccine was also given every four days in doses increasing from 250 millions to 1000 millions. The temperature chart of the first week in hospital (elsewhere) may be contrasted with that of the second week, during which treatment was in progress. (Fig. 51.)

(2) CASE LXII.—The patient, aged 29, was not admitted until the 14th day of illness. The temperature chart from the 4th day of illness is shown (Fig. 52). Treatment, therefore, was not begun until the 14th day. The patient was given eight consecutive daily doses of serum each 30 c.c. (total 240 c.c.), lumbar puncture then being performed daily for six further days before recovery was complete; vaccine was also administered in increasing doses from 250 millions to 2000 millions.

(3) CASE LXIII.—The patient, aged 26, was not admitted until the 9th day of illness. Five consecutive daily doses of serum were given
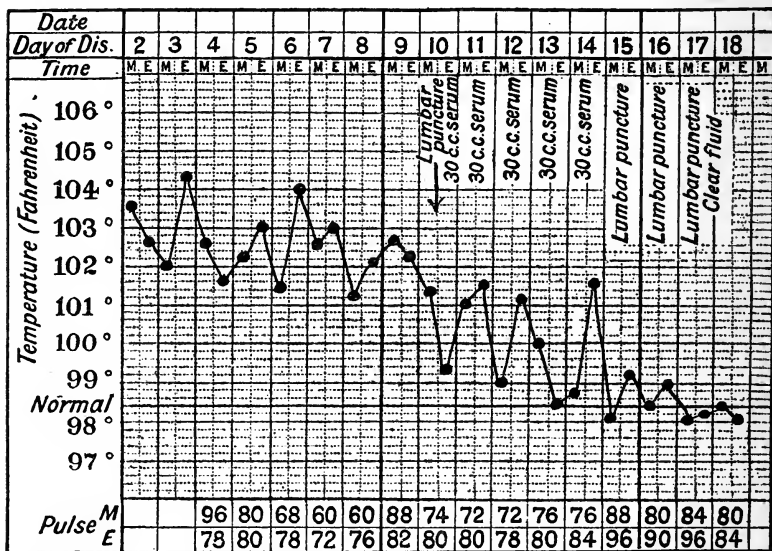
FIG. 51.—Chart of a subacute case (Case LXI. p. 435) not coming under treatment until the 10th day of illness. The difference in the course of pyrexia before and during treatment is well shown.

and lumbar puncture continued for six further days. Total course—18 days.

A cause of the protraction of the course in a subacute case may occasionally be the development of an intercurrent pneumonia as in Case XXIX. (p. 186). Other cases, however, may prove very resistant to treatment. Following the period of serum administration and consequent improvement, lumbar puncture should be continued until a clear cerebro-spinal fluid is obtained. Vaccines may be of considerable help in such cases.

Special Types.—*Progressively Purulent Type.*—In cases of this type, treatment is a very difficult problem. The patients succumb

not so much from the intensity of the infection as from the progressive accumulation of the densely purulent exudate ; conse-
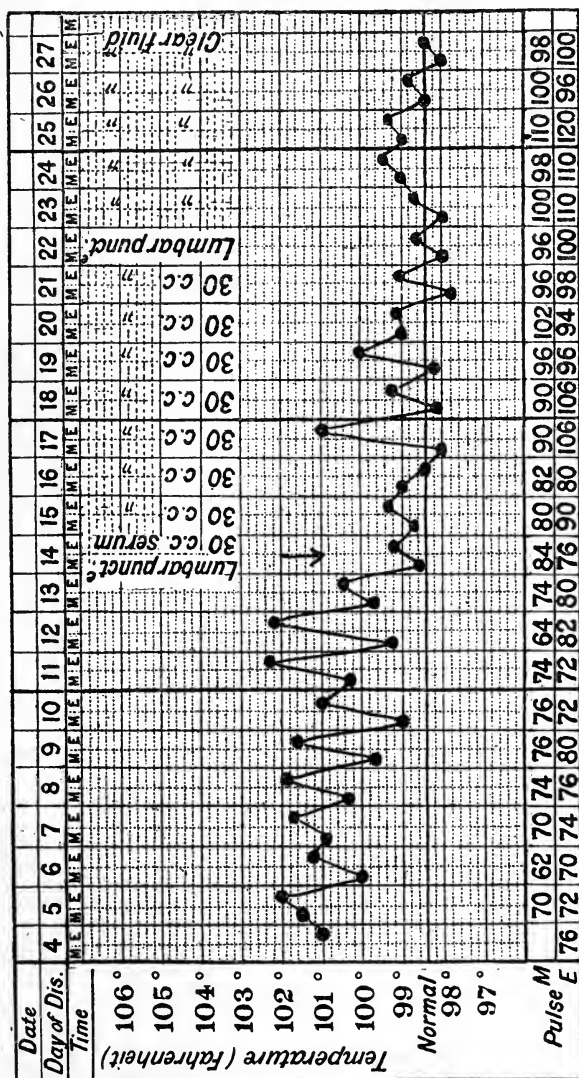
Fig. 52.—Chart of a subacute case not coming under treatment until the 14th day of illness. (Case LXII. p. 436.) The difference in the course of pyrexia before and during treatment is again well shown.

quently, the fluid becomes too thick to flow through the puncture needle, and the injection of serum under pressure is a somewhat dangerous proceeding. In view of the fact that such cases invariably prove fatal, we have tried the injection of anti-meningococcal

serum under pressure by means of a syringe, the condition of the patient carefully being watched. Small quantities of serum have been injected at frequent intervals up to three times daily ; later, the full dose—30 c.c.—was given twice daily, even though only a few c.c. of thick purulent exudate could be obtained. In no instance was any success met with. For example, in the following case, the amounts of fluid evacuated are shown in relation to the serum administered.

Day of Disease.	Cerebro-spinal Fluid.	Amount of Serum given.	Observations.
3rd	40 c.c. purulent.	30 c.c.	Fluid flowed freely.
4th	35 c.c. ,,	30 c.c.	
5th	15 c.c. thick yellow purulent.	15 c.c.	
	15 c.c. ,, ,,	30 c.c.	
6th	10 c.c. ,, ,,	10 c.c.	No fluid obtained below 2nd lumbar interspace. Puncture between 11th and 12th thoracic yielded exudate.
	5 c.c. ,, ,,	10 c.c.	
	5 c.c. ,, ,,	10 c.c.	
7th	8 c.c. ,, ,, (aspirated by means of syringe).	30 c.c. (given with syringe).	From between 1st and 2nd lumbar vertebrae.
	6 c.c. (aspirated by means of syringe).	30 c.c.	,,
8th	No fluid whatever could be obtained even by aspiration up to 11th thoracic intervertebral space.		
9th	2 c.c. aspirated, very thick pus.	10 c.c.	From between 1st and 2nd lumbar vertebrae.
10th	4 c.c.		

Meningococci were present in the cerebro-spinal fluid throughout. Post-mortem examination revealed massive purulent accumulation obscuring the structures at the base of the brain and filling the spinal subarachnoid space.

We have concluded that the injection of serum under pressure in small or massive doses is quite useless in this type of case ; it appears to have no effect upon either the clinical condition of the patient or upon the meningococci present in the pus.

Various measures have been advocated in order to start the flow of exudate.

(1) Aspiration. — A few c.cm. more of the thick exudate may be obtained by this method, but it is practically of no value except for obtaining exudate for bacteriological examination.

(2) *Irrigation with saline solution through the needle.*—Often the saline will not flow in and when a little can be persuaded to enter, no appreciable effect is produced. We have also tried sodium citrate solution with a similar result.

(3) Two needles being inserted at different levels, *e.g.* one in the interspace between the 1st lumbar and 12th thoracic vertebrae and the second in the lumbo-sacral space, saline solution is run in through the upper needle and allowed to escape by the lower. The difficulties are the same as those mentioned above ; the solution may not flow in, or even if a small quantity of exudate is washed out, no effect is produced upon the exudate in the region of the brain and upper part of the spinal cord. We have found the method of no value.

The upper puncture needle has been inserted at a higher level, *e.g.* upper dorsal or cervical region. There can, however, be no certainty that the needle enters the subarachnoid space at such a level, the spinal cord frequently being adherent to the posterior arachnoid (*vide* p. 410). Further, in very few individuals is there a continuous posterior subarachnoid space from the cervical to the lumbar region (*vide* p. 409).

(4) Cobb's method of obtaining a flow of cerebro-spinal fluid when lumbar puncture brings away a few drops only, consists of manipulating of the patient's head, under chloroform anaesthesia, with the object of breaking down possible adhesions about the foramen magnum and the floor of the fourth ventricle. We have not found this method of any assistance in progressively purulent cases.

(5) We have also tried repeated lumbar puncture, up to four times daily, as soon as the nature of the cerebro-spinal fluid suggested a possible progressively purulent type of case, but without any ultimate success as regards recovery.

Recrudescent Type.—With regard to the treatment of recrudescent types, one has to distinguish two varieties of recrudescences.

(1) Cases in which one or more recrudescences occur while the patient is actually under treatment.

(2) Cases in which the earlier part of the illness is subacute or abortive and escapes recognition as cerebro-spinal fever ; the patient appears to improve up to a certain point and then rapidly becomes worse. Specific treatment is therefore only started when the recrudescence occurs.

(1) Since adopting the method of repeated daily lumbar puncture following the period of serum administration, we have observed recrudescences in only a small percentage of cases (less than 5 per cent) and in none has more than one recrudescence occurred ; no case running a chronic course with numerous recrudescences has been met with.

The following table illustrates the treatment in three cases in which one recrudescence occurred:

TABLE XXVI

Case	1	2	3
Day of disease treatment was begun	4th	4th	2nd
Day of recrudescence	16th day	10th day	9th day
Total amount of serum given prior to recrudescence	120 c.c.	150 c.c.	150 c.c.
Total amount of serum given for treatment of recrudescence	110 c.c.	120 c.c.	120 c.c.
Days of disease (serum given and lumbar puncture performed = l.p.)—			
1	—	—	—
2	—	—	30 c.c.
3	—	—	30 c.c.
4	30 c.c.	30 c.c.	30 c.c.
5	30 c.c.	30 c.c.	30 c.c.
6	30 c.c.	30 c.c.	30 c.c.
7	30 c.c.	30 c.c.	l.p.
8	l.p.	30 c.c.	,,
9	,,	l.p.	,,
10	,,	,,	30 c.c.
11	,,	,,	30 c.c.
12	,,	30 c.c.	30 c.c.
13	,,	30 c.c.	30 c.c.
14	,,	30 c.c.	l.p.
15	,,	30 c.c.	,,
16	30 c.c.	l.p.	—
17	30 c.c.	,,	
18	30 c.c.	—	
19	20 c.c.		
20	l.p.		
21	,,		
22	,,		
Total Course	22 days	17 days	15 days

In any case that exhibits signs of developing a recrudescence of meningitis, *e.g.* the reappearance of meningococci in the cerebrospinal fluid on direct microscopical examination or on culture, reappearance of delirium or other mental change, increased muscular rigidity or pyrexia, vomiting, etc., the intrathecal injection of serum must at once be resumed until the recrudescent attack is overcome. It is most important not to confuse the occurrence of serum disease accompanied by a meningeal reaction for a recrud-

escence of meningitis (*vide* Chapter XIX. p. 466). Also, certain points with regard to the induction of anti-anaphylaxis prior to the re-administration of serum after an interval longer than 8-10 days from the last previous injection, must be observed owing to the danger of anaphylaxis (*vide* p. 470).

(2) As regards cases coming under specific treatment only with the recrudescent attack of meningitis, the treatment is the same as that for an ordinary acute or subacute case. The following illustrates the treatment given in two such cases :

CASE 1.—The initial attack was acute and abortive. The patient came under observation and treatment on the sixth day of illness, the recrudescence having occurred on the fifth day. Anti-meningococcal serum was given in doses varying from 30-45 c.c. for 12 consecutive days (total amount 325 c.c.), and lumbar puncture then repeated for seven further days before a cerebro-spinal fluid clear to the naked eye was obtained. Total course = 24 days.

CASE 2.—The acute initial attack had not been recognised as cerebro-spinal fever and the patient improved after a few days. On the sixth day, however, an acute recrudescence occurred and the case came under our observation and treatment on the seventh day. The response to serum therapy was very rapid, only four doses (each 30 c.c.) of anti-meningococcal serum being necessary ; lumbar puncture was continued for two days, following the withdrawal of serum administration, when a clear cerebro-spinal fluid was obtained. Total course = 11 days.

Chronic Types.—Cases becoming chronic may originally be acute or subacute. Since we adopted the procedure of repeated daily lumbar puncture, following the period of serum administration, until a clear fluid is obtained, we have had only one case continuing for over 30 days. This subacute case, however, had escaped recognition and consequently was not admitted under our care until the 14th day of illness. The patient recovered after a total course of 46 days ; the case has been mentioned in dealing with vaccine treatment, to which the favourable termination was apparently largely due.

Cases treated by lumbar puncture only, without the administration of serum, may become chronic ; thus, one patient aged 26, so treated, died of internal hydrocephalus after a total course of 54 days.

Chronic cases of the recrudescent type have already been dealt with, and the posterior basic type will be mentioned in connection with the treatment of hydrocephalus.

Occasionally a chronic case of meningitis may come under observation in which it is impossible to find any organisms in the cerebro-spinal fluid, either on direct examination or on culture. The fluid may be clear to the naked eye and the cytological characters resemble those found in tuberculous meningitis, viz. the number of mononuclear cells far exceeding that of the polymorphonuclears. If the case for some reason or other does not appear to be typical of tuberculous meningitis, *e.g.* owing to the history of onset or the appearance of well-marked muscular rigidities, the exhibition of anti-meningococcal serum administered intrathecally for 12 daily doses, followed by continued lumbar puncture for some days, is well worthy of trial. One case of chronic meningitis, that of a man aged 35 years, had been given practically a hopeless prognosis, the diagnosis being considered to be tuberculous meningitis. At the time he came under our observation he had been ill, at the lowest estimate, for 37 days ; there were certain features about the case which suggested a form of meningitis other than tuberculous. For instance, the onset had been somewhat acute, accompanied by vomiting ; cervical rigidity was extreme, Kernig's sign very well marked, and the cerebro-spinal fluid, though clear to the naked eye, yielded a cell count of 500 cells per c.mm., 78 per cent being polymorphonuclear and 22 mononuclear. Further, the patient had reached such an extreme degree of emaciation that it seemed to us that had the condition been tuberculous meningitis, he must have succumbed before the time he came under our observation. In view of these considerations it was thought more than likely that the case was one of chronic cerebro-spinal fever ; consequently he was treated with anti-meningococcal serum injected intrathecally, polyvalent meningococcal vaccine, and repeated lumbar puncture. The result, from almost a hopeless condition, was complete recovery. The details of the case are as follows :

CASE LXIV. *History prior to Admission.*—The patient, a man aged 35 years, came under our observation on about the 37th day of illness. According to the history obtained, the patient, more than five weeks before, had complained of severe headache one morning, which was followed later by vomiting. He was admitted to hospital where a note stated " he lay in bed on his side with a dull apathetic look, was difficult to rouse, and not able to speak—' typhoid condition.' Condition did not alter for some days. No retraction of head." Fourteen days later a further note stated " mental condition somewhat improved, but he is often dull and little or no information can be elicited from him. He seldom speaks more than a few words at a time, and sleeps

a great deal. No physical signs in lungs or abdomen.'' During this period the temperature chart showed that the case had run a somewhat irregularly intermittent pyrexia, the pulse rate varying between 88 and 112, but seldom reaching above 100 during the first week. He had vomited almost daily.

Condition on Admission.—Temperature : 100·4°, pulse 100, respirations 20. He lies on his back with all limbs in an attitude of flexion. Extremely emaciated.

Mental Condition : His mentality is occasionally quite clear as regards answers to simple questions ; at other times he relapses into a low muttering delirium. He has little or no memory for events prior to his present illness, nor is he able to give any history of the earlier part of the course.

Cranial Nerves : Pupils dilated, react well to light, no nystagmus : all other cranial nerves normal. Neck rigidity is well marked but without definite head retraction ; neck sign positive ; Kernig's sign is pronounced. Patient very tremulous. Knee jerks brisk and equal, ankle jerks brisk and equal, no ankle clonus, plantar reflexes flexor, abdominals moderate.

Incontinence of urine and faeces.

Cerebro-spinal fluid : under increased tension, clear to the naked eye, cytology 500 cells per c.mm., 78 per cent polymorphonuclear cells, 22 per cent mononuclear. No organisms seen, cultures sterile.

Wassermann negative.

Naso-pharyngeal swab—meningococci not found.

Treatment and Progress.—The patient was given ten consecutive daily doses of anti-meningococcal (polyvalent) serum (38th to 46th days inclusive), vaccine also being administered—250 millions (38th day), 500 millions (41st day), and 1000 millions (45th day). At the end of this period of serum treatment the condition was as follows. His memory for past events had much improved, although he still exhibited frequent delirium ; incontinence had practically ceased, vomiting was entirely absent, the pupils were no longer dilated, he was less tremulous, neck rigidity and Kernig's sign were both well marked.

Following the cessation of serum administration, lumbar puncture was performed daily for nine days (47th to 55th days inclusive), as much cerebro-spinal fluid as possible being withdrawn at each operation. Vaccine was also continued in increasingly larger doses—1500 millions (49th day), 2000 millions (53rd day), and 2500 millions (57th day). At the end of this period the patient's mental condition had greatly improved ; he was able to converse; his memory not only for past events but also for recent events was considerably better. No vomiting or incontinence had recurred, and neck rigidity was decidedly less. The fluid obtained at the last lumbar puncture showed only 30 lymphocytes per c.mm.

From this time onwards the patient's progress was one of rapid improvement, although from time to time he exhibited interesting and

peculiar periods of mental aberration. He gradually gained flesh, and the muscular rigidities slowly disappeared. Finally, two months after the beginning of the course of treatment, his mental condition was perfectly normal and he was up and about the ward. Eventually, recovery was complete.

Treatment in Relation to Type of Infecting Coccus

When the type of meningococcus obtained from a patient's cerebro-spinal fluid has been determined by the agglutination test (p. 18), an anti-serum, in the production of which that particular type of organism is known to have been used, should be employed for the intrathecal injection. Failing a knowledge of the source of the serum, the agglutinating power and opsonic reaction towards the particular type of meningococcus isolated should be tested. Although, as pointed out previously (p. 397), these tests are of limited value, in the present state of our knowledge it is safer to discard a serum showing little or no agglutination towards the type of coccus concerned in the infection. Gordon's method of testing the immune serum for anti-endotoxin is apparently a more reliable test of therapeutic activity (p. 402). When no organisms can be cultivated from the cerebro-spinal fluid, they may frequently be obtained from a naso-pharyngeal swab, if taken early in the disease, for the purpose of determining the type.

The Lister Institute have now prepared univalent sera for each of Gordon's four types of meningococcus, as well as a polyvalent sera valent for all four types. The method of administration is to inject the polyvalent serum at the initial lumbar puncture and until the type of infecting coccus is determined, and then replace it by the serum univalent for the particular type.

As regards vaccine therapy, a polyvalent meningococcal vaccine (including the four types) is given until a growth of meningococci is obtained from the cerebro-spinal fluid; autogenous vaccine is then prepared and substituted for the polyvalent. Univalent vaccines for each of Gordon's four types we have also prepared for use in the absence of an autogenous vaccine.

Type I. coccus is the most resistant to the therapeutic sera at present in use and appears to give rise clinically to a more severe form of disease. Forty-three cases, in which it was possible to determine the type and which were treated by means of an anti-meningococcal serum, yield the following figures:

	No. of Cases.	Recovered.	Died.	Mortality.
Type I. coccus .	10	4	6	60 per cent
Type II. ,, .	20	14	6	30 ,,
Type III. ,, .	10	6	4	40 ,,
Type IV. ,, .	1	—	1	—
Atypical . . .	2 [1]	2	—	—

[1] Of these, one case occurred before Type IV. was differentiated by Gordon.

General Management and Treatment of Symptoms

The ward or room chosen should be isolated and be provided with an abundance of fresh air. Nurses should be specially experienced in the disease as careful nursing is of paramount importance. In the case of adult men patients male attendants are necessary, not only for maintaining the patients in the requisite position during the operation of lumbar puncture, but also for keeping those delirious and violent in bed ; sitting up or getting out of bed is not only undesirable but dangerous for the patient. The bed should be comfortable and the head of the patient be kept fairly low, not more than one pillow being allowed. On admission to hospital the hair is cropped close to the scalp. Unconscious patients should be turned frequently and not permitted to lie in the same position for hours at a time ; this is of considerable importance as hypostasis is undoubtedly a predisposing factor in the development of pneumonia in cerebro-spinal fever cases. Sophian considers that pneumonia can be avoided in a fair percentage of cases if sufficient care be taken to avoid hypostasis. In all severe cases tending to run a course of longer than about ten days, it is desirable that a water-bed should be substituted for the ordinary mattress, as, unless this precaution be taken, difficulty with bed sores may be experienced. Care should be taken to see that the patient is not suffering from overflow retention of urine ; if necessary the catheter must be used twice daily.

As regards the transport of patients, in our experience the danger is negligible. Many of our cases have been brought by motor ambulance distances of 20 or more miles ; no ill effects attributable to the journey were ever observed.

Diet.—The diet given should be as full as is consistent with the digestive capacity. As a rule, the digestive functions are not greatly disturbed in cerebro-spinal fever, and the appetite is often well maintained. In the early acute stage milk, beef essences,

cocoa, etc., are given; as soon as possible, semi-solids—custard, bread and milk, minced under-done mutton—should be allowed. There is no need to wait for the disappearance of pyrexia before ordering a fish diet; patients are hungry and take food well towards the end of the course. From fish with the ordinary vegetables, cases are put on chicken. Water, lemonade, etc., are given freely throughout the course of illness.

If stupor be present nasal feeding may be resorted to; feeds are given four times in the 24 hours and, according to age, consist of from 5 to 15 ozs. of citrated milk (sodium citrate, grs. 2 per oz. of milk) diluted with an equal part of water. Beef extracts may also be given occasionally. When vomiting is present, peptonised milk or whey and albumin water may be administered.

As regards infants, Goeppert showed that the prognosis was rather better in breast-fed infants than in those bottle-fed; consequently, if possible, it is desirable to continue breast feeding. The mother must of course be isolated.

Bowels.— As with most febrile diseases, constipation is the general rule. To counteract this, calomel or castor oil may be given at night, followed by a saline purge next morning. Liquid extract of cascara, pulv. glycyrrhizae co. are also useful; nevertheless, it is frequently necessary to order an enema.

The excreta, as well as discharges arising from conjunctivitis and herpetic eruptions, should be subjected to disinfection.

Symptoms.—For the relief of headache, phenacetin (grs. 10) with caffeine (grs. 2) may be given and repeated twice daily: cold applications may also be of benefit. Acetyl-salicylic acid (grs. 15) will frequently relieve muscular pain and that occurring in the back and legs after serum administration. As a routine measure we give grs. 10 of acetyl-salicylic acid after each intrathecal injection of serum.

To allay mild vomiting not due to hydrocephalus, the following mixture will be found useful:

Hydrocyanic acid dil.	.	.	.	♏ 15
Liquor. morph. hydrochlor.	.	.	.	♏ 5
Sod. bicarb.	.	.	.	grs. 10
Aq. chloroform ad.	.	.	.	℥ 1

The most efficacious measure for the prevention of vomiting, however, is continued daily lumbar puncture. In the series of cases we have treated by the method previously described, vomiting was very infrequent.

Sulphonal (grs. 20-30) will be found useful in promoting sleep. For obstinate insomnia or when delirium with restlessness is present, morphine (grs. ¼) should be given and repeated if necessary. As a rule, no difficulty is experienced in discontinuing this drug in cerebro-spinal fever patients.

When morphine fails to alleviate the restlessness of delirium, potassium bromide (grs. 10-20, according to age) has sometimes given good results; it may also be given in combination with chloral.

Paraldehyde is of little value in the delirium of cerebro-spinal fever, and hyoscine should be avoided. Warm sponging and occasional warm packs may also assist in relieving restlessness.

Should symptoms of cardiac failure or a falling blood pressure develop, hot saline infusions (temperature = 100° F.) should be given either rectally or subcutaneously in the pectoral regions every 8-12 hours. Digitalin gr. $\frac{1}{100}$ hypodermically can also be given often with good results. Strychnine, owing to its liability to precipitate convulsions, should not be administered.

The importance of fresh air cannot be too strongly insisted upon. If the day was sufficiently warm we often placed the patients in the open air ; those tending to run a long course invariably seemed to benefit. As cerebro - spinal fever is an exhausting disease, patients should remain in bed for at least 10-14 days after the termination of the course.

Treatment of the Naso-Pharynx.—As soon as the condition of the patient permits, measures should be taken to free the naso-pharynx from meningococci ; this is important as relapses are probably due to a reabsorption of organisms from this situation. Elsewhere (p. 378) we have shown that meningococci may persist in the naso-pharynx for some time after recovery from the disease has taken place. Sterilisation may be effected by directing the patient to sniff a warm solution of 1 per cent chloramine into the nostrils from the palm of the hand, expelling it through the mouth. This is repeated twice daily under personal supervision until three successive naso-pharyngeal swabs have proved negative.

Treatment of Complications

Septicaemia.—Cases in which meningococci are cultivated from the blood stream in the presence of definite meningitis, should be given anti-meningococcal serum intravenously as well as intra-thecally in doses of 30-40 c.c. In spite of the bad prognosis in such cases, instances of recovery have been reported following the

above method of treatment, one by Bovaird and another by Netter.

The treatment of the bacteriaemic stage preceding meningitis has already been dealt with (*vide* p. 403).

Pneumonia.—Pneumonia is treated on the usual lines. The occurrence of this complication is no indication for stopping the intrathecal administration of serum. Lumbar puncture, etc., should be continued daily as before. In Case XXIX. (p. 186) this procedure was carried out and, in spite of the presence of lobar pneumonia, recovery took place.

Arthropathies.—As a rule arthropathies subside fairly quickly with simple immobilisation and warm applications. If considerable distension is present the joint should be aspirated and 5-10 c.c. of anti-meningococcal serum injected; even when the arthropathy has been present for some time, this procedure usually results in prompt recovery.

Pyelitis and Cystitis.—When pyelitis or cystitis develops, hexamine should be given in doses of 10-15 grs. thrice daily. We have used the following mixture:

Hexamine	.	.	.	grs. 10
Sodii acid phosph.	.	.	.	grs. 10
Syrupi aurantii	.	.	.	℥ 1
Aq. ad.	.	.	.	℥ 1

℥ 1 t.d.s. in a wine-glassful of water.

The same procedure may be adopted if meningococci are isolated from the urine.

Should cystitis co-exist with retention of urine, the bladder is best washed out twice daily with boracic solution.

Hydrocephalus.—The generalised hydrocephalus occurring during the early stages of meningitis is relieved by the lumbar puncture preliminary to the first injection of serum. As much cerebro-spinal fluid as possible should be withdrawn.

Hydrocephalic symptoms developing later in the course are treated by repeated lumbar puncture, the operation if necessary being performed twice daily. Continued daily lumbar puncture following the period of serum administration largely counteracts any tendency towards the development of hydrocephalus; nevertheless, symptoms of this complication occasionally occur. Continued lumbar puncture, however, will often bring about complete relief as, for example, in the following case:

CASE LXV.—A subacute case, aged 29, and not received until the

14th day of illness, was given anti-meningococcal serum in 30-c.c. doses each day for eight days. For two days following this only small amounts (5-10 c.c.) of cerebro-spinal fluid were obtainable on lumbar puncture ; as a result, the patient developed symptoms of hydro-cephalus—apathy, vomiting, incontinence, tremulousness, dilated pupils, and marked head retraction : no organisms were visible in the cerebro-spinal fluid nor obtainable on culture. With repeated daily lumbar puncture, however, larger quantities of fluid (50-70 c.c.) were gradually obtained and the hydrocephalic symptoms disappeared. The patient was punctured on nine successive days, following the termination of the period of serum administration, before a perfectly clear cerebro-spinal fluid was withdrawn. The total course of illness amounted to 30 days.

In a few cases, symptoms of hydrocephalus may appear in spite of the fact that fair quantities of cerebro-spinal fluid are withdrawn daily. When this occurs, lumbar puncture should be performed both morning and evening until the hydrocephalic symptoms have disappeared ; if the cerebro-spinal fluid is only slightly turbid and no organisms have reappeared, serum administration need not be resumed. Case XLII. (p. 212) illustrates the relief afforded by this treatment.

Internal Hydrocephalus.—When internal hydrocephalus develops in infants (posterior basic types), as evidenced by " dry taps " on lumbar puncture and the usual physical signs, treatment can only be effective if directed to drainage of the ventricles. The method of puncture is as follows :

The upper part of the scalp having been shaved and the skin sterilised, the anterior fontanelle is defined and an ordinary lumbar puncture needle with stylet placed at the lateral angle, that is about one inch ($2\frac{1}{2}$ cm.) from the mid-line. The needle is pointed in a direction downwards, slightly backwards and inwards, and is pushed in to a depth of about $1\frac{1}{4}$ inches (3 cm.). When the ventricles are very dilated and the cerebral cortex thinned, the needle entering in almost any direction will usually strike fluid.

The operation is usually well borne and the amount of shock small. There are two possible dangers—injury to vital centres and haemorrhage. The risk, however, is very small and the gravity of the condition warrants the procedure.

At the first operation cerebro-spinal fluid should merely be withdrawn. If this fluid reveals no meningococci either on direct examination or culture, subsequent punctures should consist in the simple removal of fluid. If, however, the fluid proves to be

infected, serum should be injected, the administration being carried out in the same way as in intraspinal injection and the same precautions observed.

The amount of fluid withdrawn should, of course, be considerably less than the quantity of serum administered.

Both ventricles are tapped preferably on alternate days ; if puncture be confined to one ventricle, the drainage of the other is incomplete.

In older children and adults trephining is necessary. Two methods are available :

(1) *Keen's Method.*—The trephine opening is made at a point $1\frac{1}{4}$ inches (3 cms.) above the external auditory meatus ; this site corresponds with the posterior end of the temporal line and is known as Keen's point. In performing the puncture, the needle is directed towards the upper limit of the opposite pinna. At a depth of about 2 inches (5 cm.), the lateral ventricle will be entered at its widest part, that is, where the lateral and posterior horns are given off from the body at the posterior end of the optic thalamus. The most dependent part of the ventricle is tapped by this method, thus affording more adequate drainage than if it were entered from above.

W. J. Denehy found that in nine cases coming to autopsy, the lateral ventricles having previously been tapped by Keen's method, no damage to the brain substance had occurred. In each case the puncture pierced the most dependent part of the lateral ventricle. The slightly blood-stained needle track was easily identified, but even in the case of multiple puncture there was no serious damage to the brain. In one case a blood clot lay extradurally immediately within the skull, due to the accidental rupture of a vessel.

(2) *Kocher's Method.*—A point one inch ($2\frac{1}{2}$ cm.) from the midline and about $1\frac{1}{2}$ inches (4 cm.) anterior to the bregma, is taken as the situation for performing the trephine. In puncturing, the needle should be directed downwards and backwards ; the ventricle will be reached at a depth of $1\frac{1}{2}$ to 2 inches. There is practically no risk of haemorrhage during the passage of the needle.

Whichever of the above methods be adopted, one side should be operated on first and the other subsequently. When internal hydrocephalus is present, the dura will be found tense and non-pulsating. On withdrawing the stylet from the puncture needle the fluid usually escapes with force and should be allowed to escape until the flow ceases.

Unfortunately, it cannot be claimed that ventricular puncture in internal hydrocephalus is a striking success, as recoveries are relatively few. Nevertheless, excepting in very rare cases already mentioned (*vide* p. 227), the operation offers the only chance of avoiding a fatal issue. Our experiences coincide with those of Fairley and Stewart, viz. that in most instances the patient's life was prolonged but the cases terminated fatally. Several cases, however, have been reported in which infected ventricular fluid has been removed and replaced by anti-meningococcal serum, to be followed by complete recovery. Cases, including intraventricular puncture in infants, are recorded by Cushing and Sladen, L. Fischer, Sophian, Netter and Debré, Levy, Bouché, Syer White, Neveu-Lemaire, Debeyre and Rouvière, de Verbizier and Chauvel, Triboulet, Roland and Fenestre, Korkweg and Gardner Robb.

Paralyses.—When flaccid paralysis of a lower neurone type develops, care should be taken to avoid over-stretching of the paralysed muscles by the use of suitable appliances. Thus, in paralysis affecting the extensors of the wrist and fingers, the hand should be supported by a splint designed to counteract drop-wrist ; similarly in the case of drop-foot. Massage and passive movements should be instituted as soon as possible ; in muscles reacting to the faradic current, faradism should be applied. When response to this form of electrical stimulus is absent, galvanism should be employed.

In paralysis of an upper neurone type, massage and movements will assist in keeping the paralysed muscles in good condition ; care, also, should be taken to counteract as far as possible any tendency to contractures.

Conjunctivitis.—Conjunctivitis, in our experience, is best treated by means of the following lotion applied 3-4 times in the 24 hours—Equal parts of a saturated solution of boracic acid and a 1 in 2500 solution of mercury perchloride ; prior to use, one part of the lotion is mixed with an equal quantity of warm water.

Irido-Choroiditis.—Netter has recorded two instances of suppurative irido-choroiditis in which the intravitreous injection of anti-meningococcal serum is stated to have led to the prompt abatement of inflammation. Sight was retained.

Deafness of Central Origin.—For this unfortunate complication little can be done. Potassium iodide is often given, without, however, any definite results.

Other Methods of Treatment

Human Serum.—M'Kenzie and Martin, in 1908, observed that fresh human serum contained certain thermo-labile substances which had a distinct inhibitory effect on the growth of meningococci. The serum from cases of cerebro-spinal fever, particularly convalescent patients, contained a larger proportion of these substances. The actual bacteriological effects, in M'Kenzie and Martin's experiments, were shown largely to depend on the complement contained in the serum. Accordingly, these observers employed fresh human serum, injected intrathecally, in 16 acute cases of cerebro-spinal fever ; 10 recovered (mortality 38 per cent). The doses given varied from 15 to 20 c.c.

More recently, serum obtained from the patient himself as well as from recovered cases has occasionally been injected intrathecally. For instance, Foster and Gaskell mention one case—that of a man who having recovered from all acute symptoms, suffered from irregular attacks of pyrexia accompanied by headache. Five c.c. of his own blood serum were injected intrathecally and complete relief of all his symptoms ensued. Allan obtained serum from a patient who had recovered from an acute attack of cerebro-spinal fever and injected it intrathecally into a patient suffering from the same disease ; the result is said to have been almost dramatic, the symptoms largely abating within a few hours. The dose and frequency of administration, however, are not stated.

In one of our patients, 18 c.c. of his own blood serum, withdrawn the previous day, were given intrathecally on the 11th day of illness. The case was of a severe type, the meningitis having improved considerably up till the 8th day, when a recrudescence appeared. The case occurred in 1915 when the brand of anti-meningococcal serum available was not altogether satisfactory. The injection of autogenous serum was followed by a fall in temperature from 103° to 99·6° on the afternoon of the following day, accompanied by a slight temporary improvement in the general condition ; the patient died, however, on the 16th day.

Owing to the complete absence of complement in the cerebro-spinal fluid, no trace being found in 1·5 c.c. of several samples, Fairley and Stewart considered that much of the useful bacteriotropic action of the commercial anti-meningococcal serum was rendered inoperative or ineffective, horse serum also being very poor in this substance. Consequently these observers adopted a

modification of M'Kenzie and Martin's method which they term " complement reinforcement of anti-meningococcal serum." Five c.c. of blood from a convalescent case of cerebro-spinal fever is mixed with 20 c.c. of anti-meningococcal serum. Since such small quantities of human serum were used, any increased value of the reinforced serum over that of the ordinary anti-meningococcal serum, they consider, is attributable rather to the addition of complement than to specific antibody. The danger of conveying syphilitic infection is avoided by performing a Wassermann test on all human serum used. Of ten acute cases so treated, seven recovered and three died. Of four chronic cases, three recovered and one died ; these, however, were also treated with vaccine and potassium iodide. The mortality of the acute cases, therefore, was 30 per cent ; in other similar cases treated with the same serum without complement reinforcement, the mortality was 50 per cent. Fairley and Stewart consider that the method of reinforced serum therapy is superior to the ordinary serum treatment.

Repeated Lumbar Puncture without Serum Injection.—Prior to the introduction of a specific immune serum, repeated simple lumbar puncture was used extensively. Although it was recognised as a definite advance, the results as regards mortality were far from satisfactory. In two of the greatest epidemics in the history of the disease, viz. the New York epidemic of 1904–1905 and that of Prussia in 1905–1907, despite the use of repeated lumbar puncture, the mortality rate remained as high as ever. In the Silesian epidemic, also, Goeppert showed that the mortality was not lowered by the use of lumbar puncture alone.

Owing to the comparative failure of many of the therapeutic sera supplied in England early in 1915, Foster and Gaskell were led to readvocate simple repeated lumbar puncture without serum administration. Of 30 cases so treated 21 recovered.

In cases we treated by this method during 1915, the results were not encouraging ; the disease, in many instances, tended to run a protracted course with the ultimate development of internal hydrocephalus.

Lavage of Intrathecal Sac.—Attempts have been made to wash out the intrathecal space by means of saline solution, distilled water, etc. ; such methods, however, are not to be recommended. In those of our earlier cases in which this was attempted, no beneficial results were observed. In cases of the progressively purulent

type, saline and sodium citrate solutions were equally ineffective. Further, the giving of repeated intrathecal injections of fluid within a few minutes of each other is not free from risk, owing to the fall in blood pressure produced thereby. The amount of fluid run in can seldom be recovered in anything approaching the same quantity, with the result that when an attempt is made to administer serum very little will enter.

Drugs injected intravenously or intramuscularly.—*Formaldehyde.*—In 1900 Maguire advocated the intravenous injection of formaldehyde in the treatment of pulmonary tuberculosis. In his opinion 50 c.c. of a 1 in 800 solution of formalin (1 in 2000 of formaldehyde) was the upper limit of safety. Fairley and Stewart applied the same treatment to cerebro-spinal fever. Up to two hours after injection, however, no formaldehyde could be detected in the cerebro-spinal fluid.

Soamin.—This drug, having proved of some value in trypanosomiasis, was tried as a remedy for cerebro-spinal fever. In 1910 T. Arnold Johnson reported two cases of cerebro-spinal fever in which he administered soamin intravenously ; both cases recovered. Later, in 1913, Shiroore and Ross employed the drug during an epidemic of the disease in British East Africa ; these authors treated 127 cases by means of intramuscular injections. The usual dose of soamin was 5 grains. Many cases received only one dose, while in others it was repeated on 1-3 occasions. In the majority of cases one or two lumbar punctures also appear to have been performed. Nevertheless, even excluding 37 cases termed malignant and dying within 60 hours of the onset, only 56 of the remaining 90 recovered. Subsequently, the drug was also used, in the same locality, by Gilks and Butler with no very striking results.

In several cases during 1915 we gave soamin intravenously in 5-grain doses, but were not able to trace any benefit directly to its action. Further, administration of the drug is known in some cases to lead to optic atrophy.

Antimony Tartrate.—Sheffield Neave treated six cases by means of intravenous injections of antimony tartrate. 1·5 c.c. of a 2 per cent solution were used as an initial dose ; in later doses, if necessary, the amount was gradually increased up to 6 c.c. In one case the patient had had a period of three weeks daily remitting temperature after the main nervous symptoms had subsided ; within 48 hours of a single injection the temperature became

normal and so remained, the patient making an uninterrupted recovery. In two fulminating cases the drug had no effect on the disease, but two others, it is stated, aborted a few hours afterwards in a remarkable way. Elsewhere, however, in the same report the passage appears : " No case with haemorrhagic patches recovered."

In four cases a small dose was given intrathecally without any satisfactory result.

Other Drugs.—Salvarsan, neosalvarsan, or intramine have all been given in a few cases without definite benefit. Hexamine and helmitol have also been employed intravenously (*vide* p. 458).

Although drugs such as soamin, antimony tartrate, salvarsan, etc., might conceivably do good in septicaemic cases, there is no evidence, either clinical or experimental, to lead to the supposition that they influence meningitis. The drugs are unable to reach the subarachnoid space, as the choroid plexus offers an impenetrable barrier to their entry into the cerebro-spinal fluid.

Intrathecal Injection of various Chemical Substances.—In 1902, during an epidemic at Lisbon, Seager reported favourably on the use of lysol administered intrathecally. The first results, however, were not confirmed by later observers. Subsequently, Wolff recommended the intraspinal injection of 0·2 per cent protargol. Sheffield Neave tried lavage of the intrathecal sac with a solution of 0·5 per cent carbolic acid in normal saline, but was unable definitely to trace any improvement to its use. The experience of A. C. E. Gray with intrathecal injections of flavine was distinctly unfavourable. More recently, dilute solutions of eusol have been suggested ; in one of our earlier cases eusol did not prevent a fatal issue.

Flexner and Amoss, in 1916, studied the effects of lysol and protargol in the treatment of experimental meningococcal infections in young guinea-pigs and monkeys. Neither substance proved to have any curative action on the experimental peritoneal infection of guinea-pigs, and protargol showed no therapeutic power in subarachnoid meningococcal infections in the monkey. On the contrary, these observers point out that both drugs, in their influence on leucocytes, are anti-leucotactic and anti-phagocytic ; also, they are potent protoplasmic poisons. Recovery from meningococcal infection, both in man and laboratory animals, is accomplished chiefly by phagocytosis. Specific anti-meningococcal serum acts curatively by increasing leucocytic emigration, directly promoting phagocytosis, and neutralising bacterial endotoxin. Lysol and protargol have none of these actions. Hence whatever bacteri-

cidal advantage drugs possess, it is more than counteracted by the harmful effects they cause.

Ponticaccia, after administering serum to a patient without apparent benefit, gave 5 c.c. of hydrogen peroxide intrathecally. This was followed by a diminution in pyrexia, the temperature remaining low for two and a half days. On the day following this, the symptoms returned and another peroxide injection was given with good effect. Finally, after a third dose of 2·5 c.c., the patient is said to have improved steadily.

Hexamine and helmitol, as described in the next section, have also been administered intrathecally.

Hexamine (Hexamethylene Tetramine). Syn. Urotropine.— This substance, first prepared by Butlerow in 1860, was introduced into therapeutics in 1894 by Nicolaier. Chemically, it is a condensation product obtained by the action of ammonia on formaldehyde. It is readily soluble in water, and in the presence of acids is dissociated into ammonia and formaldehyde. The equilibrium point varies with the degree of acidity, the temperature, and possibly in body fluids, with the organic constituents of the solution.

Since it was shown by Crowe in 1909 that hexamine was one of the few drugs excreted into the cerebro-spinal fluid, its use has been widely advocated in all forms of meningitis, as well as in cases in which meningeal infection is threatened. It is known, however, that the antiseptic properties of the drug depend entirely upon its partial dissociation into formaldehyde, hexamine itself possessing no such action. The question, therefore, is whether free formaldehyde is liberated after such secretion into the cerebro-spinal fluid. Dissociation, however, apart from temperatures above 50° C., only takes place in an acid medium. It was shown by Fairley and Strathy in France that the addition of hexamine to an alkaline medium containing organisms had no inhibitory effect on the growth of the organisms, but in an acid medium of 1 to 600 dilution, hexamine showed a complete inhibitory action.- The first question therefore is : In meningitis, is the cerebro-spinal fluid acid or alkaline ? It has been shown in Chapter X. (p. 243) that in cerebro-spinal fever the cerebro-spinal fluid is alkaline in the vast majority of cases. Fairley and Stewart, in fact, were unable to trace any acidity in the pathological cerebro-spinal fluids from cases of the disease with litmus and Henderson's reagent. By the use of phenolphthalein, however, in the method described in Chapter X. (p. 244), we were able to show that in a small percentage of cases,

during the acute stage, the cerebro-spinal fluid may be very faintly acid.

The second question is : What evidence is there that the hexamine secreted into the cerebro-spinal fluid dissociates with liberation of free formaldehyde ? Unfortunately, the chemical problem of detecting formaldehyde in the presence of hexamine is one of considerable difficulty, as most of the reagents used in testing for the former substance in solution, cause decomposition of the hexamine with the consequent liberation of formaldehyde. Solutions of hexamine, therefore, respond to most of the tests for formaldehyde. By the Burnham-Ramini test, however, one is enabled to/ discriminate between true formaldehyde and that combined in hexamine. The test is carried out as follows :

The solution to be tested is warmed to slightly above body temperature, and three drops each of the following solutions added :

      (1) Phenyl-hydrazine hydrochloride   .   0·5 per cent.
      (2) Sodium intro-prusside ·   .   .   0·5 per cent.

A few drops of a saturated solution of sodium hydrate are then poured down the side of the test tube.

If formaldehyde be present, a greenish-black colour appears and rapidly changes to green, pale green, orange, and finally yellow. The test is said to detect formaldehyde in dilutions from 1 in 150,000 upwards, but does not show the reaction with hexamine. In solutions stronger than 1 in 20,000, an intense dark-blue colour appears prior to the green.

If the test is negative, a fresh sample of the fluid to be examined should be boiled after the addition of a few drops of sulphuric acid. The test is then applied in the same manner. If formaldehyde be present, the fluid has contained hexamine.

The presence of hexamine in solution can also be demonstrated by Hehner's test :

Hehner's reagent consists of 100 c.c. of 90 per cent sulphuric acid with one drop of 3 per cent ferric chloride solution. To clear cerebrospinal fluid (if turbid it should be filtered), a few drops of milk are added, or a very small amount of casein. This mixture is then stratified with an equal volume of Hehner's reagent. If hexamine is present a deep amethyst coloration develops at the junction of the two layers. If hexamine or formaldehyde is present in too great a concentration, the colour reaction may not occur without dilution.

Liebermann's formaldehyde test we have found unreliable for work with cerebro-spinal fluid.

Fairley and Strathy found that hexamine, when administered by the mouth, was invariably excreted by the cerebro-spinal fluid ; by the Burnham-Ramini test, however, they were unable at any time to detect the presence of free formaldehyde. Fairley and Stewart, in Australia, using the same test, also failed to find formaldehyde in the cerebro-spinal fluid from cases of cerebro-spinal fever in which doses up to 60 grs. of hexamine had been administered intravenously ; the presence of hexamine up to four hours after injection was demonstrated by means of Hehner's test. It was also shown that hexamine, when added to the cerebro-spinal fluid from cases of cerebro-spinal fever in amounts far exceeding any concentration attainable by therapeutic administration, did not exert any inhibitory action on the growth of the meningococci.

In a series of observations, we were able to confirm the fact that hexamine, when given by the mouth in cases of cerebro-spinal fever, is excreted into the cerebro-spinal fluid. Also, at no time were we able to demonstrate the presence of free formaldehyde by means of the Burnham-Ramini test, even when the fluid was neutral or very faintly acid. In common with most other observers, we found that, clinically, no definite benefit could be traced to the action of the drug.

Hexamine was administered not only by the mouth, but also intravenously and intrathecally, in 20 cases of cerebro-spinal fever by Guest and Fairley, without any beneficial result ; the mortality of the cases was fully 80 per cent. No ill effects attributable to the hexamine were observed when doses of 60 grs. were given intravenously in normal saline. Intrathecally, the drug was injected in doses of 20-60 grs. dissolved in saline solution or horse serum.

Helmitol (Hexamethylene tetramine anhydromethylene citrate). —Owing to the poor results obtained with hexamine, and also to the fact that it dissociated only in an acid medium, Fairley and Stewart abandoned its use in favour of helmitol, an allied drug, which, however, liberates formaldehyde in alkaline as well as in acid media. Its use as a substitute for hexamine had previously been advocated in 1914 by Thomson Walker. Fairley, in experiments in vitro, found that helmitol exerted a definite inhibitory effect on the growth of meningococci. The concentration of helmitol, however, was much greater than would ever be possible in the human body. The drug was then tried as a therapeutic measure in about 30 cases of cerebro-spinal fever. It was found that when 60 grains were given intravenously, helmitol could be demonstrated in the

cerebro-spinal fluid, by means of Hehner's and Liebermann's tests, within half an hour of administration. Fifteen grs. administered by the mouth every 24 hours kept the cerebro-spinal fluid continuously under helmitol influence. In no case, however, was it possible to demonstrate the presence of free formaldehyde by means of the Burnham-Ramini test ; the observers were compelled to assume, therefore, that formaldehyde was either absent or not present in sufficient concentration to be detected (1 in 150,000 in non-albuminous urine).

Clinically, owing to the limited number of cases treated, the value of helmitol was difficult to estimate and no very definite conclusions were reached.

Helmitol dissolved in normal saline or horse serum (10-30 grs. to an oz.) was also injected intrathecally by Fairley and Stewart in 10 cases of cerebro-spinal fever. The only danger appears to be that of the helmitol containing pre-formed formaldehyde ; consequently, the drug should be treated with absolute alcohol to dissolve out any formaldehyde present. Also, the solution should be fresh and contained in an alkali-free glass receptacle. One case developed flaccid paraplegia with loss of sensation and incontinence of urine, due, apparently, to a neuritis of the cauda equina. Six of the ten cases treated recovered.

From a consideration of the above facts, it is clear that no definite value can be attached to helmitol in the treatment of cerebro-spinal fever. If any result is to be expected from the use of a drug of the hexamethylene tetramine group as a cerebro-spinal antiseptic, it would seem that helmitol is more satisfactory than hexamine.

Venesection.—In acute cases with symptoms of respiratory failure, which Fairley and Stewart consider is due to cerebral hyperaemia, venesection combined with the application of cold to the head has been advocated. The above authors also maintain that lumbar puncture should not be performed when the patient is comatose immediately preceding a respiratory failure, nor when respiratory failure has occurred, since the effect of the withdrawal of cerebro-spinal fluid is to lower the pressure in the subarachnoid space and so allow the cerebral hyperaemia to increase.

Surgical Methods of Treatment.—In addition to the operative measures designed for the relief of internal hydrocephalus, the following surgical methods of treatment may be mentioned. Haynes, in 1912, advocated suboccipital decompression, with the idea of

securing permanent drainage of the cisterna magna. Although his three cases, said to be in a hopeless condition before operation, died, they are stated to have been distinctly relieved by the procedure. Bourke, Abraham and Rowlands submitted to decompression four cases not progressing favourably; the dura mater was opened only in the presence of bulging (one case). Three cases died and one recovered. The areas of trephining were as follows: left Rolandic, left temporo-parietal, right frontal, and subtemporal regions. Cases proving fatal died nine hours after operation in two cases, and ten days afterwards in the last.

H. D. Rolleston and H. W. Allingham, in 1899, reported a case treated by laminectomy and incision of the dura mater in the thoracic region; although great difficulty was experienced in stopping the flow of cerebro-spinal fluid when the symptoms had subsided, the patient eventually recovered. Heiman and Feldstein state that laminectomy, incision of the occipital ligament and craniotomy, with through-and-through drainage, has also been attempted.

CHAPTER XIX

SERUM disease, first described under this name by von Pirquet and Schick, results from the introduction into the circulation of a serum foreign to the organism concerned.

It has been supposed that serum disease occurs rather more frequently after intrathecal injections of serum than after subcutaneous injections. Flexner estimated that sero-toxic phenomena were observed in 70 per cent of cases of cerebro-spinal fever recovering or surviving the first injection for more than ten days. In cases occurring in the Royal Navy during the first three years of war and treated with various brands of serum, H. D. Rolleston states that 41 per cent developed a serum rash ; during the third year of war the figure was 58-60 per cent. Of our own cases recovering or surviving longer than ten days, serum disease occurred in 55 per cent. As regards subcutaneous injections, Currie, in 50 cases of cerebro-spinal fever treated chiefly by subcutaneous injections of serum (13 received one intrathecal injection, the remaining doses being given subcutaneously), found that 58 per cent developed a serum rash. Goodall, in 8726 cases of diphtheria treated with serum administered subcutaneously, observed rashes in 40 per cent. H. D. Rolleston quotes the figures shown by cases of diphtheria treated with serum in the hospitals of the Metropolitan Asylums Board during the years 1898 to 1903, viz. 37,277 cases, 44 per cent of which developed serum disease. J. D. Rolleston, in cases of diphtheria in which a serum rash was specially watched for, found the condition in 67-81 per cent.

It will be seen, therefore, that it is very doubtful if it can be maintained that the intrathecal injection of serum is more liable to be followed by serum disease. Certain brands of serum, it

would appear, are more often associated with serum disease than others ; also, the symptoms are seen less often in infants than in older children and adults. Goodall's figures for cases of diphtheria suggest that the condition may occur more frequently in females than in males, *e.g.* 32·6 per cent males and 37·1 per cent females.

Symptoms.—The commonest manifestation of serum disease is the occurrence of a rash. It usually appears on the 8th-10th day following the initial dose of serum ; less frequently it occurs earlier or much later. The earliest rash observed in our series of cerebro-spinal fever cases appeared on the 5th day and the latest on the 16th day following the first dose of serum. In cases of diphtheria, the latent period has been known to vary from 3 to 22 days, the most frequent interval, however, being 8-10 days.

The rash, as a rule, is either urticarial or erythematous, or a combination of both.   The erythema is marginate, circinate or occurs in irregular blotches. Very rarely the rash is petechial or purpuric, and cases exhibiting vesiculae or bullae have been described.   As regards distribution, the rash is more or less general following intrathecal injections, but occasionally it may be limited to the trunk or extremities.   The duration of the eruption is variable ; it may persist from a few hours to some days, but the average duration is about two days.

Occasionally two separate rashes, the second occurring after an interval during which the skin is free from eruption, are observed. The rashes may both be urticarial or erythematous, or one the former and the other the latter ; as a rule, the first is urticarial and the second erythematous. When the initial rash fades and again becomes prominent a day or two later, it is probable that the two are phases of the same reaction. The longest interval between two serum rashes observed by Goodall was 12 days, while H. D. Rolleston mentions a case in which the two rashes were separated by an interval of 15 days. The occurrence of two distinct rashes and even three, separated by a long interval, has been known to follow a single injection of serum. According to Dale and Hartley, the explanation is as follows : Each of two different proteins in the serum can produce a separate reaction, the latent period of these reactions differing in length of time.

In many cases, arthralgia is complained of, while in a few, definite synovial effusion occurs. The joints most often affected are the knees and wrists, less frequently the elbows, shoulders and hips, and very occasionally the smaller joints of the hands

and feet. According to Goodall, even the temporo-maxillary and sterno-clavicular joints have been affected in cases of diphtheria treated with serum. Transient albuminuria, diarrhoea and cervical and inguinal adenitis are also not infrequent. The symptoms usually last from 2 to 4 days (*vide* Figs. 53 and 54).
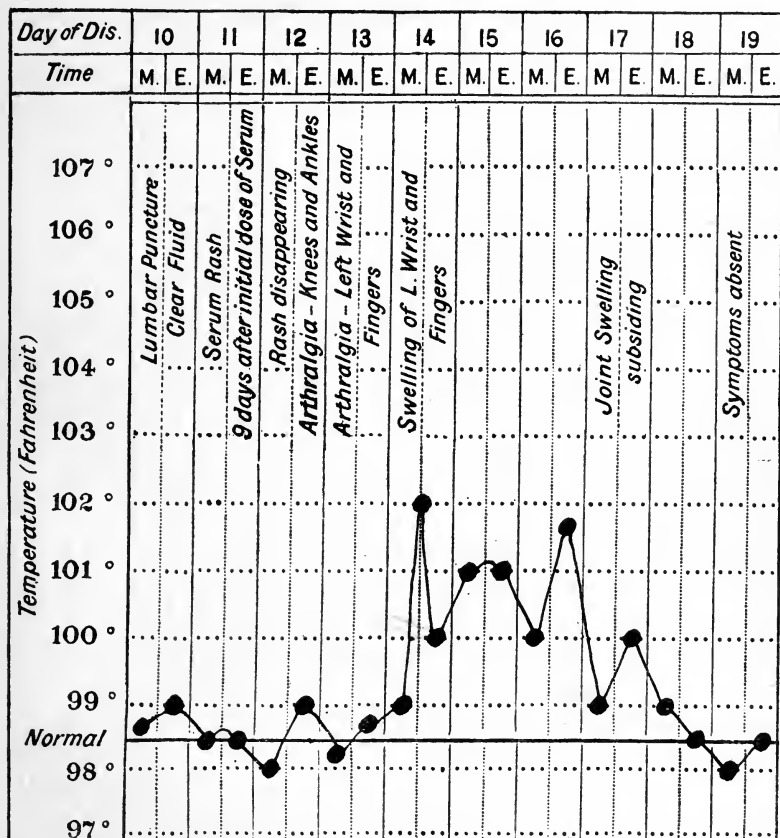
FIG. 53.—Pyrexia accompanying Serum Disease. Acute case of cerebro-spinal fever recovering after a ten days' course. Symptoms of serum disease appeared nine days after initial dose of serum (45 c.c.). (*Vide* p. 465.)

In many cases pyrexia occurs, and in our experience usually follows the disappearance of the rash. As regards serum disease in cases of cerebro-spinal fever, the rise of temperature shows a characteristic curve, the duration being from 2 to 4 days (*vide* Figs. 53 and 54). Diarrhoea may follow closely upon the serum rash and, in turn, be succeeded by synovial effusion and pyrexia.

Arthralgia or joint effusion may precede or be accompanied by pyrexia, but only seldom have we observed pyrexia precede the other symptoms.

It is extremely probable that a rise in temperature of relatively short duration may be the only manifestation of serum disease.
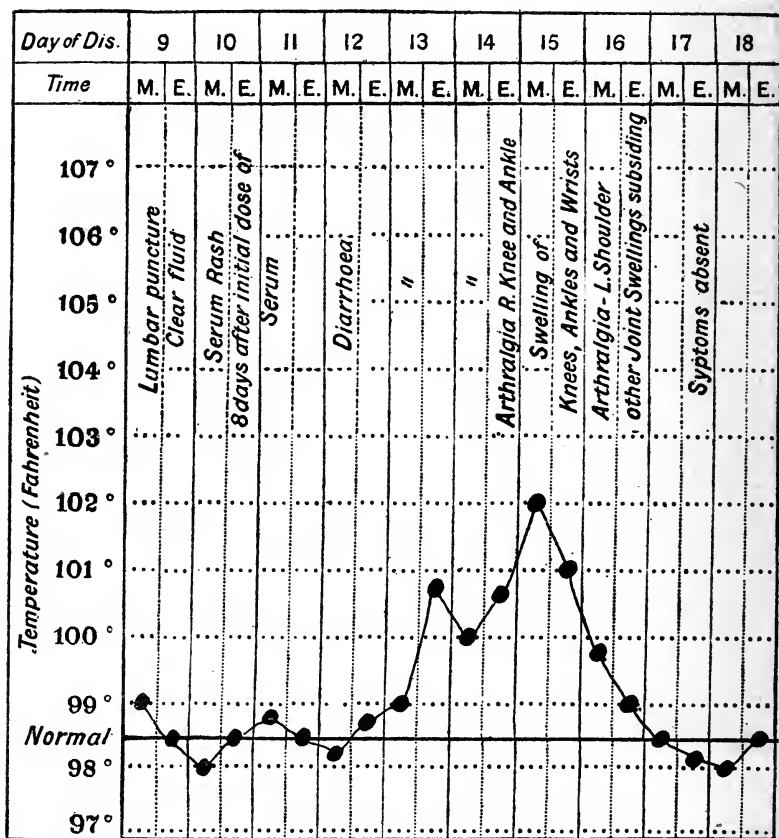
FIG. 54.—Pyrexia accompanying Serum Disease. Acute case recovering after a ten days' course. Symptoms of serum disease appeared eight days after initial dose of serum (30 c.c.). (*Vide* p. 465.)

This is obviously difficult to prove in cases of meningitis, but we have observed an apparently characteristic pyrexia occur on the 8th-10th day following the initial dose of serum in mild subacute cases whose meningitis, as exhibited by a clear cerebro-spinal fluid, etc., terminated on the 6th or 7th day, and in which there was nothing to suggest a recrudescence (*vide* Fig. 55).

The following two examples illustrate the more severe manifestations of serum disease :

(1) *Acute Case* (Fig. 53)—

      Initial dose of serum 45 c.c.

      Total dosage of serum 135 c.c. extending over four days.

9 days following initial dose.	Rash (urticaria + erythema).
10 ,, ,, ,,	Rash disappeared. Pain in knees, ankle, left wrist and fingers. Temperature (normal for 3 days) rose in afternoon to 102° F., falling to 100° during evening.
11 ,, ,, ,,	Swelling of left wrist and fingers. T. 101°.
12 ,, ,, ,,	Swelling less.
13 ,, ,, ,,	Swelling absent.
14 ,, ,, ,,	Subsidence. Temperature normal.

(2) *Acute Case* (Fig. 54)—

      Initial dose of serum 30 c.c.

      Total dosage of serum 150 c.c. extending over five days.

8 days following initial dose.	Rash (erythema) on inner side of thighs.
9 ,, ,, ,,	Rash universal (urticaria + erythema).
10 ,, ,, ,,	Rash faded. Diarrhoea in evening (10 motions).
11 ,, ,, ,,	Diarrhoea continued (14 motions in 24 hrs.). Evening temperature (previously normal) = 101° F.
12 ,, ,, ,,	Diarrhoea ceased. Pain in both knees and right ankle. Right knee swollen in evening. T. = 99·2°-101°.
13 ,, ,, ,,	Swelling of both knees, right ankle and both wrists, left shoulder painful.
14 ,, ,, ,,	All subsided excepting left wrist. Temperature fell to normal in evening.
15 ,, ,, ,,	All symptoms absent.

Among the rarer symptoms of serum sickness are oedema of the tongue, scrotum and penis. We have observed congestion of the fauces with an oedematous uvula, but oedema of the glottis is extremely rare. Sophian mentions one case of pulmonary oedema, while Rosenhaupt, in 1905, reported a case of serum disease in which there was pericardial effusion. Transient haematuria has also been described.

In a few cases of cerebro-spinal fever, serum disease may appear in the form of a meningeal reaction ; this selective localisation, according to Netter and Debré, is due to meningeal oedema occurring in the previously inflamed tissues owing, no doubt, to the lack of resistance, and is analogous to swelling of the fauces in the serum disease of diphtheria. In 58 cases of cerebro-spinal fever developing serum disease, H. D. Rolleston states that in 9 cases (15·5 per cent) the serum rash was preceded or accompanied by a recrudescence of meningeal symptoms.
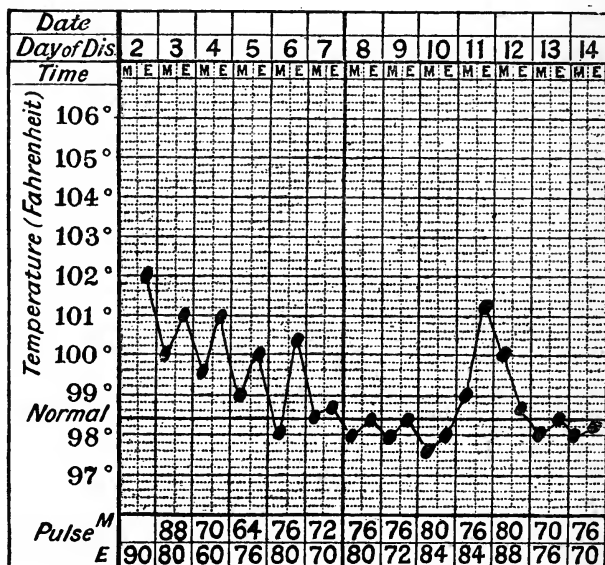
FIG. 55.—Subacute case (mild) exhibiting a rise of temperature on the 10th day following the initial dose (30 c.c.) of anti-meningococcal serum—presumably a manifestation of serum disease. There were no other symptoms.

Care must be taken not to mistake the meningeal reaction of serum disease and the pyrexia accompanying it for a recrudescence of meningitis, as the injection of a large volume of serum may be attended by serious results from anaphylaxis. Neck rigidity and Kernig's sign, having disappeared, may reappear or, if still present, become increased, but, bearing in mind the date of expected serum disease, points of distinction are as follows : If meningitis has passed off, lumbar puncture will reveal a clear fluid containing relatively few cells ; in the absence of a recrudescence, no meningococci will be found on direct examination of films. In serum

disease, on testing the cerebro-spinal fluid, glucose will be found present, while it is absent with a recrudescence of meningitis. Further, as pointed out previously (pp. 293-296), an increase in the white cells of the blood almost invariably accompanies a recrudescence, while in serum disease no change occurs.

The following case illustrates meningism as a symptom of serum disease :

CASE LXVI. (Fig. 56).—The patient, aged 18, was admitted on the 4th day of illness. The onset had occurred suddenly with head-

Date																												
Day of Dis.	4		5		6		7		8		9		10		11		12		13		14		15		16		17		18
Pulse M	72	72	88	88	96	96	96	100	104	92	90	72	96	76	80
E	68	80	80	84	88	92	92	110	92	94	80	100	92	72	84
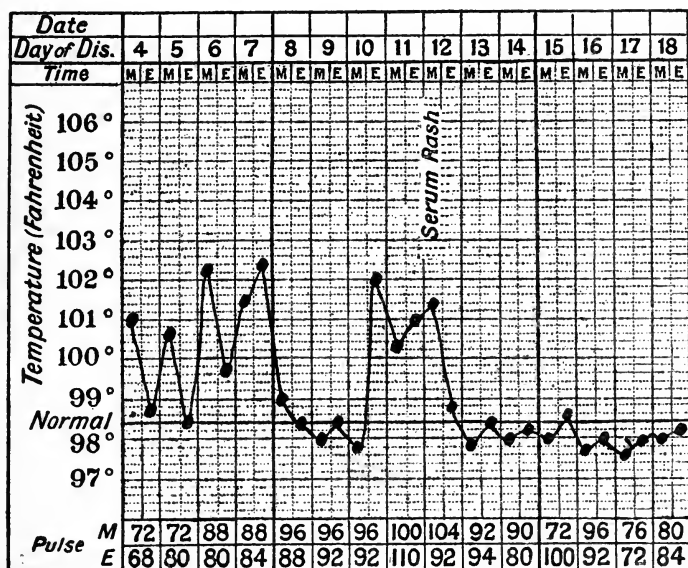
FIG. 56.—Chart of Case LXVI. in which meningism occurred as a symptom of serum disease (Case LXVI. p. 467).

ache, vertigo and vomiting, following a period of malaise of about two weeks' duration and consisting of " cold " and " sore throat."   On admission, the patient was somewhat delirious and neck rigidity and Kernig's sign were well marked ; lumbar puncture revealed a turbid fluid containing meningococci.

Thirty c.c. of serum were given on each of the first five days in hospital (4th-8th days of illness inclusive). On the 8th day (5th dose of serum) the temperature reached normal and remained normal throughout the following (9th) day. The patient had greatly improved, his mental condition being normal, muscular rigidity considerably less, and the cerebro-spinal fluid being almost clear. Meningococci had been seen in the fluid obtained on the 5th day but not in subsequent fluids.

Consequently, after the 8th day, serum injection was stopped, lumbar puncture alone being performed. On the evening of the 10th day the temperature rose to 103° F.; on the following day (11th) pyrexia was still present, and both neck rigidity and Kernig's sign had increased. Lumbar puncture, however, revealed a fluid almost clear, containing polymorphonuclear cells and several mononuclears but no organisms. The glucose reaction was well marked. Next day (12th) an urticarial serum rash appeared and the meningitic symptoms had improved; lumbar puncture continued to show a fluid almost clear to the naked eye and towards evening the pyrexia declined. On the 13th day the temperature remained normal, and on the 14th the cerebro-spinal fluid was quite clear to the naked eye.

Relation of Serum Disease to Amount of Serum administered.— According to Weaver, J. D. Rolleston and others, the frequency of serum disease varies directly with the volume of serum injected. As regards intrathecal injections of serum in cerebro-spinal fever, it is true that the larger doses (40-45 c.c.) are usually followed by serum disease, but we have not found any constant relation between the intensity of the reaction and the dose of serum given. Serum disease following a dose of serum of 40-45 c.c. was often no more intense, and often much less, than that seen in cases receiving an initial dose of 30 c.c. Similarly, well-marked reactions may occur in cases to whom a first dose of only 15-20 c.c. is administered.

The total amount of serum also bears no definite relation to the severity of the subsequent serum disease. Thus, a well-marked reaction, with urticarial rash and in some instances synovial effusion, occurred in several cases receiving only 120 c.c., the initial dose being 30 c.c., while no manifestation of serum disease was ever observed in one case to whom 600 c.c. (initial dose also 30 c.c.) were administered. In a few cases, however, in which serum injection is continued, a second serum rash may appear, and we have observed three separate rashes occur at different times in the same case.

Treatment of Serum Disease.—For the milder forms of rash no treatment is necessary as the eruption quickly fades. The irritation of an intense urticarial rash may be relieved by bathing with a warm solution of sodium bicarbonate or the local application of 1 per cent menthol solution. As regards the treatment of synovitis and the more severe forms of oedema, $\frac{1}{2}$ to 1 c.c. of pituitrin may be injected subcutaneously. This appears to act quickly in relieving the symptoms; for instance, in a case exhibiting congestion of the fauces and oedema of the uvula, $\frac{1}{2}$ c.c. of pituitrin

(P. D. & Co.) was injected at 11 P.M. on the day of the appearance of the throat symptoms and repeated at 5 A.M. on the following morning ; by 10 A.M. all signs were absent. In another case an intense and universal serum rash appeared at 7 P.M. ; $\frac{1}{2}$ c.c. of pituitrin was given at 11 P.M. and repeated at 5 A.M. on the following day. The rash had completely disappeared when the patient was seen at 9 A.M.

Anaphylaxis.—The phenomenon of an attack of serum disease almost immediately following an injection of serum given several days or weeks after a first dose, was recorded in 1896 by Hartnung (two cases) and Denys and Leclef (one case). In 1902 Richet observed that in animals, the injection of a protein substance foreign to the organism concerned was followed in a few days by certain symptoms, and further, that when the injection was repeated several days later, the symptoms reappeared in a more intense form ; the first injection of protein, far from rendering the animal immune to the toxic effects of a second dose, had rendered it more sensitive. To this condition of increased sensibility, Richet applied the term " anaphylaxis," meaning the reverse of prophylaxis. Similar observations on animals were also published by Arthus in 1903. In 1905 von Pirquet and Schick described in detail the clinical phenomena of serum disease and correlated them with the experimental work of Richet and Arthus ; they also emphasised the fact that when an interval of at least ten days exists between the primary injection and the second injection, serious symptoms are liable to follow the latter. That is, an abnormal reaction is to be expected when the interval between the two injections is longer than the latent period of the usual serum reaction. When, however, a series of injections are made at intervals of a few days, abnormal reactions are not observed ; such cases were investigated by Currie, in 1907, who found that the phenomena associated with anaphylaxis did not occur after any of the serial injections.

The condition of anaphylaxis is therefore one of increased susceptibility to the toxic effects of a protein substance, brought about by the introduction of that substance into the tissues. To produce anaphylactic symptoms, the same protein (*e.g.* serum-globulin or serum-albumin) must be employed for the secondary injection as was used for the primary. Whereas a small dose will sensitise a person or animal, a large dose is usually necessary to give rise to symptoms of anaphylaxis. The route of introduction also plays some part. When injected intravenously, a smaller dose of the

protein substance produces symptoms of anaphylaxis than is the case when it is introduced subcutaneously.

There is no available evidence as to how long a person remains sensitive to serum injections following the expiration of the latent period of the usual reaction. E. W. Goodall mentions one case still sensitive after seven years, while Waugh records a fatal case of anaphylaxis in a girl, aged 17, who died five minutes after an injection of diphtheria antitoxin ; ten years earlier she had also suffered from diphtheria and received an " injection."

Not every individual to whom a primary injection of serum is given becomes sensitised. Goodall found that 36 per cent (74 of 203) of re-injected individuals showed no symptoms of anaphylaxis.

The symptoms due to anaphylaxis which may follow the reactive dose of serum are classified by Goodall as follows :

(1) A shortened latent period (under one week) with the usual symptoms of ordinary serum disease.

(2) A very severe attack, usually after a very short latent period, consisting of profuse urticaria, oedema of the mucous membranes of the mouth, nose, larynx and pharynx, respiratory embarrassment and occasionally vomiting, pyrexia and synovial effusion.

(3) An immediate reaction with rigors, muscular twitchings, cyanosis, dyspnoea, vomiting and collapse. An urticarial rash may precede, accompany or follow these symptoms ; occasionally pyrexia, diarrhoea or convulsions may occur, and as a rule severe prostration persists for some time.

In rare instances (1 in 50,000), patients may exhibit anaphylaxis without any primary injection of serum. Most of the fatal cases reported are of this type. The reaction is immediate and the symptoms approximate to those described above under (3). Convulsions are usually present, followed by coma, death occurring from respiratory failure while the heart is still beating. The condition is said to be more common in asthmatic subjects and especially those whose asthma is excited by emanations from horses.

Anti-Anaphylaxis. — When an individual has recovered from anaphylactic symptoms brought about by a secondary dose of serum, a further injection, given after a short interval, fails to produce any reactionary symptoms ; the patient is evidently de-sensitised. A similar condition results from repeated daily injection and also when a small dose of serum, known as the desensitising dose, is given a few hours before the larger dose. Consequently,

if in a case of cerebro-spinal fever it is decided to resume serum administration after an interval of longer than ten days from the primary dose, and the patient has not received any serum for some days, anti-anaphylaxis should be induced prior to the injection of the usual therapeutic dose. The following method of inducing anti-anaphylaxis, based on the work of Besredka and Friedberger, is described by C. H. Browning :

Five c.c. of the serum it is proposed to inject are diluted with 50 c.c. of normal saline. Of this mixture 1 c.c. is injected intravenously, followed by 3 c.c. four minutes later, 10 c.c. after another two minutes, and finally 25 c.c. after two further minutes. The dilute serum is best administered by means of a graduated funnel attached to the intravenous needle by a rubber tube ; the latter can be pinched for the requisite intervals during the injection.

Fifteen minutes after the above injections have been given, the full therapeutic dose of serum may be administered. In the vast majority of cases no untoward symptoms will result.

Intrathecal injections, it may be added, are less dangerous than intravenous in producing severe symptoms of anaphylaxis. It is possible that owing to the fact that the serum does not escape from the subarachnoid space into the general circulation quite so quickly as when introduced directly into a vein, some degree of desensitisation is produced during the process of absorption.

As Goodall remarks, there is some reason to believe that the condition of anti-anaphylaxis is not permanent and in some individuals is transient and even absent. In one case of cerebro-spinal fever coming under our observation no anti-anaphylactic phase could be detected. The patient, aged 20, was seen on the 21st day of illness ; he had received a 30-c.c. dose of serum on each of the fourth, fifth, sixth, and seventh days of illness ; therefore, on the day mentioned above (21st), no serum had been administered for 14 days, and an interval of 12 days had elapsed since the primary injection. As the lumbar puncture revealed a turbid fluid containing a few meningococci and the patient was said to have shown no improvement, further serum injection was indicated. Accordingly, an attempt was made to induce anti-anaphylaxis by the method described above. While the final 25 c.c. of dilute serum was being administered, the patient suddenly developed an intense urticarial rash, distributed over the face, arms and trunk, followed immediately by twitchings of the hands, arms and facial muscles, cyanosis, loss of consciousness, and rapid and feeble pulse. Fifteen minutes

later, rigors and vomiting occurred, followed by marked prostration. In view of these serious symptoms, it was considered desirable to ascertain if the patient was desensitised before proceeding to inject a large dose of serum. Consequently, half an hour after recovery from the rigors and vomiting, 3 c.c. of the dilute serum was injected, followed four minutes later by 10 c.c.; during this latter injection the identical symptoms recurred—intense urticaria, muscular twitchings, cyanosis, feeble pulse and loss of consciousness. Further attempts at testing the patient's sensitivity after intervals of two days (23rd day) and ten days (31st) were attended by exactly similar results.

Treatment of Anaphylaxis.—At present little definite is known concerning the exact mode of production of the phenomena associated with anaphylaxis. Since, however, the more severe symptoms can be referred to the vagus nerve (irritation) and the sympathetic nervous system (depression), it is reasonable to endeavour to counteract them by the exhibition of drugs which tend to depress the vagus and stimulate the sympathetic system. Therefore, on the occurrence of severe anaphylactic symptoms, atropine (up to $\frac{1}{50}$ gr.) and adrenalin (5-10 minims of a 1 in 1000 solution) should be injected intravenously.

CHAPTER XX

PRIOR to the introduction of repeated lumbar puncture and the intrathecal administration of specific anti-meningococcal serum as routine measures in the treatment of cerebro-spinal fever, many of the relatively few cases that recovered appear to have suffered from some permanent disability, either mental or physical. The older writings on the subject abound with references to the frequency of infirmities met with in survivors from the disease. Some allowance, however, must be made for the fact that owing to the absence of accurate diagnosis by an examination of the cerebro-spinal fluid obtained on lumbar puncture, the so-called meningeal form of acute anterior poliomyelitis and particularly polioencephalitis, were often confused with meningitis ; consequently, many of the paralytic sequelae of the former diseases were erroneously attributed to meningitis. Nevertheless, serious disabilities frequently followed cerebro-spinal fever, by reason, no doubt, of the compression to which the brain structures were subjected, during the course of the disease, by the increased tension of cerebro-spinal fluid unrelieved by lumbar puncture. Contrary to popular supposition, it is an undoubted fact that in recent years serious sequelae have been considerably less frequent than formerly. These improved results are due not only to the relief of intracranial pressure afforded by repeated lumbar puncture, but also to the shortening in length of the usual course of the disease, occasioned by the use of anti-meningococcal serum administered intrathecally.

In infants, as formerly, the sequelae remain the most serious. Batten, for instance, writing in 1915, states that in the endemic form affecting infants and occurring annually in London, only 15 per cent of cases recover completely ; 35 per cent survive but exhibit some permanent defect—either mental impairment, hemiplegia, diplegia, or blindness, while the remaining 50 per cent

prove fatal.   In infants, internal hydrocephalus is a most frequent complication, its development and course being considerably modified by the anatomical condition of the infantile cranium ; the intracranial pressure, brought about by the accumulation of cerebro-spinal fluid in the ventricles, not only leads to compression of the cerebral tissues but also expends itself in producing bulging of the fontanelles and separation of the cranial sutures.   In the infant, therefore, the nervous structures of the cerebral cortex are subjected to a considerably more *gradual* pressure than is the case when, as in the adult, the cranial capacity is a fixed quantity. These facts may account for the occurrence in children of permanent disabilities such as diplegia, blindness of central origin, mental impairment, at the present time observed only very rarely in adults.

The following description of the conditions of nervous origin which may result from an attack of cerebro-spinal fever, is based chiefly upon a study of a series of 120 recovered cases coming under the authors' observation.

MENTAL CHANGES

In the adult mental impairment is very rare.   During 1915–17, of 120 patients recovered from cerebro-spinal fever, mainly adolescents and adults, we met with no instance in which permanent mental enfeeblement resulted.   Bourke, Abraham and Rowlands, however, state that of 77 military cases recovering from the disease (1915), feeble-mindedness was present in two.

Among the minor psychical changes, Netter mentions conditions of irritability and puerility, while other French authors describe marked loss of attention or memory, moroseness, morbid shyness and morbid egoism.   During early convalescence, we have observed that some patients may exhibit unevenness of temper, anger being easily evoked, while inability to concentrate the attention for any length of time is relatively frequent.   Such changes rarely persist, but disappear after a variable period.

Puerility occurred in one case of 120, the patient, aged 23 years, having survived a severe attack of the disease, the duration of which was approximately 40 days.   When first beginning to walk about, this patient would attempt to carry out practically anything he was told to perform, no matter how absurd it might appear, *e.g.* walking on his hands and knees, lying under the bed, etc. After a week or two, however, he recovered his normal mental equilibrium.

Three patients of the 120 recovered cases complained of defects of memory. The first, seen three months after discharge from hospital, stated that he had occasional difficulty in remembering things that were told to him or orders it was his duty to carry out. A second patient, four weeks after the termination of the course of illness, complained that he had forgotten the names of several of his intimate friends and also of places he had visited. When seen a year later, his memory had greatly improved but he considered that he could not remember facts as well as prior to his illness. The third patient was employed in clerical duty at a military depot; on returning to work, he found that he had great difficulty in adding up columns of figures that previously he had managed with ease: no other psychical symptoms were complained of. Six months later his defect was still present.

Foster and Gaskell mention one recovered case in which there was complete loss of memory; as a concomitant paralysis of the right arm was present, however, the amnesia possibly owed its origin to a definite and localised cortical lesion. Six months later this patient's memory was almost completely restored, although some weakness of the arm persisted.

As regards permanent mental defects following the disease in infants, Looft estimated that 3·7 per cent of 539 idiots owed their condition to an attack of meningitis. Netter, without doubt rightly, attributes a considerable number of such cases to insufficient sero-therapy. Cases in which dementia results are often suffering from chronic hydrocephalus, which, in some instances, may persist for a considerable period. In all cases with dementia care should be taken to exclude hydrocephalus, even though apparent recovery from meningitis has occurred, before the patient leaves hospital.

SENSORY SYMPTOMS

Headache. — Patients may continue to complain of headache for some time after convalescence is established and Kernig's sign is definitely absent. In the majority of cases this symptom entirely disappears after a few months; in others, however, it persists for longer. Of the 120 recovered cases already mentioned, only eight continued to suffer from headache three months after becoming convalescent; a few stated that the symptom only occurred after exertion, and in one case it was merely nocturnal.

Persistent headache of a severe nature is sometimes due to a

certain degree of hydrocephalus, which later may give rise to serious symptoms and even produce a fatal result (*vide* p. 216).

Pain in the Back.—Pain, weakness, and stiffness in the back are almost invariable complaints during the early stages of convalescence ; in consequence, an awkward gait may persist for some weeks. The majority of patients cease to experience backache about 3-4 months after the termination of the course of illness. Several, however, may complain of weakness in the back for many months after recovery ; in some the symptom is only noticed on stooping, while in others pain is present in damp weather. Hyperaesthesia of the spine may occasionally persist well into convalescence.

That the pain and weakness in the back are due to the effect of the disease itself rather than to that of lumbar puncture, is shown by an observation by Foster and Gaskell. A certain case in which lumbar puncture was performed once only, owing to the presence of auricular fibrillation, recovered completely from meningitis after a course of about 40 days ; the patient, however, exhibited the symptom of pain in the back to a greater degree than other cases on whom a dozen or more punctures had been performed. Also, we have known cases recovering from an abortive attack of the disease, who had had no more than one or two punctures, complain of pain and weakness in the back for a longer period than patients who had passed through a severe illness necessitating the performance of many lumbar punctures. In all recovered cases, we have carried out an examination for possible lesions of the cauda equina resulting from repeated lumbar puncture ; of upwards of 120 cases, however, in no single instance could the slightest lesion be demonstrated.

Pain in the Limbs.—Pain in the legs persisting for more than three months after recovery is a comparatively rare sequel. Occasional pain was complained of in two only of the 120 cases, the leading question not being put. Only one patient volunteered the information that he experienced occasional pain in the arms.

MOTOR DEFECTS

Ocular Muscles.—As lesions of the nerves supplying the muscles of the eyeball usually improve coincidently with recovery from meningitis, permanent strabismus as a sequel is most uncommon. When present, it is usually the result of involvement of the sixth cranial nerve.

Of the 120 cases only two exhibited an ocular palsy persisting for longer than three months after recovery from the disease. The first patient, who during the attack of cerebro-spinal fever had had complete paralysis of both external rectus muscles, exhibited, when seen three months after his discharge from hospital, complete paralysis of the left external rectus, while some weakness still remained of that on the right. The second patient, examined six months after recovery, showed nystagmus and marked weakness of one external rectus muscle.

Bourke, Abraham and Rowlands, of 77 cases recovering, met two with permanent strabismus.

As a rule the pupils remain somewhat dilated for some weeks after the establishment of convalescence, but eventually become normal. Persistent myosis or inequality in the size of the two pupils is extremely rare. Permanent nystagmus also is most infrequent.

Limb Palsies.—Paralysis of limbs, developing during the course of the disease, may persist for several months after recovery from meningitis. Monoplegias due to the involvement of spinal nerve-roots almost always disappear eventually, although a considerable time may elapse before function is fully restored. In Case XXXVII. (p. 199), for instance, which exhibited a lower neurone paresis of the right arm, full power was recovered in the affected limb about seven months after recovery from meningitis. Hemiplegia, occurring as a complication of cerebro-spinal fever, often terminates in almost if not quite complete recovery. In one of our cases (Case XII., *vide* p. 164), in which hemiplegia developed about the 51st day of illness, the arm rapidly became normal. Seven and a half months later all that remained of the lower limb palsy was weakness of the calf muscles and inability to flex or extend the great toe ; the other toes exhibited weak movement. Both patellar clonus and ankle clonus, previously present, had disappeared, but on the affected side the knee jerk and tendo Achillis jerk remained brisker than those of the opposite limb, and the plantar reflex was still extensor.

Cerebral haemorrhage, occurring during the course of cerebro-spinal fever in middle-aged patients with pre-existing nephritis, or softening of the internal capsule may lead, if the patient recovers, to permanent hemiplegia. This condition was present in one patient (Case XXXVI. p. 198) seen 12 months after recovery from an acute attack of cerebro-spinal fever. Flaccid paraplegia,

fortunately a very rare complication, may show some improvement but is usually permanent.

Some degree of weakness in the legs and unsteadiness of gait is frequent during the early stages of convalescence. In a few instances, according to Sophian, exaggerated knee jerks associated with a true ankle clonus and extensor plantar reflexes may be elicited. We have frequently observed ataxia with a positive Romberg's sign and difficulty in walking; in many cases exaggeration of the deep reflexes is also present. In no instance, however, in the absence of a definite upper neurone lesion have we found ataxia with either definite ankle clonus or an extensor plantar reflex. Romberg's sign was not observed in any case in which a period of one month had elapsed from the time of the patient's beginning to walk.

One man, aged 30, was met with who had had an attack of cerebro-spinal fever at Belfast eight years previously; for a considerable period following his recovery he had complained of weakness affecting the legs. When examined, he stated that he still felt weak and " shaky " in the legs after moderate exertion; he exhibited, however, no abnormal physical signs.

Peripheral Neuritis.—This condition is a very rare complication of cerebro-spinal fever; of two cases seen in which definite neuritis affected the lower extremities, complete reaction to degeneration in the muscles supplied by the affected nerves developed in neither case. In one case the tendon reflexes were beginning to return and sensation was nearly normal within three months of recovery from meningitis; the second patient, after a similar period, exhibited normal cutaneous sensation, but both the knee and ankle jerks were still absent and the vibration sense much diminished.

Muscular Rigidity.—Rigidity of the cervical muscles persisting for any considerable period after recovery is extremely rare. As a rule, neck rigidity is absent within a few days to a week of the cerebro-spinal fluid returning to normal. In Case XI. (p. 110), however, actual head retraction persisted long after the disappearance of meningitis. One month after the termination of the course, the patient having been up and about for over a week, there was still a tendency to head retraction with inability to bring the head quite into the vertical position. Massage, etc., was then instituted and 4 weeks later there was some improvement; he remained, however, unable to flex the head beyond the perpendicular while standing in the erect position. Finally, it was not until $3\frac{1}{2}$ further

months had elapsed (5½ months from the termination of the course of meningitis) that the patient was able to flex the head sufficiently for the chin to reach the chest.

Kernig's sign, in the majority of cases, persists for the first 5-14 days of convalescence. In a few cases the sign may still be present for 20 or even 30 days following the evacuation of normal cerebro-spinal fluid and in the absence of all symptoms of hydrocephalus. Some rigidity of the hamstring muscles can occasionally be demonstrated 2-3 months after recovery.

OTHER NERVOUS CONDITIONS

Aphasia.—Persistent aphasia has been noted in rare instances. One case of our series in which this complication occurred (Case IV., *vide* p. 203) had fully recovered the faculty of speech before the termination of the course of the disease. In Case XXXVI. (p. 198) a certain degree of motor aphasia accompanied a persistent hemiplegia.

Epilepsy.—Sainton mentions epilepsy as a rare but occasional sequel of recovery from cerebro - spinal fever. This observer describes one case in which the crisis began with an aura of gastric origin—nausea and vomiting, followed by loss of consciousness and epileptic convulsions. The cerebro-spinal fluid between the crises was normal, but the fluid obtained immediately after the seizure showed a slight lymphocytosis. The general condition of the patient was good. Voison reports a somewhat similar case.

Petit mal is also stated occasionally to occur.

Neurasthenia.—Considering the severity of the usual course of the disease-process in cerebro-spinal fever, we have found the occurrence of true neurasthenia following recovery from the disease surprisingly uncommon. It is contended by Dejerine and others that to constitute true neurasthenia, in addition to a state of neural fatigue, there must exist a condition of continued emotivity ; the non-adaptation of a continuous emotive cause, to which is often added an obsessing preoccupation, produces a condition of neural exhaustion, and the sum total of the phenomena resulting justifies a diagnosis of true neurasthenia.

The appearance of neurasthenia following recovery from cerebro-spinal fever, therefore, would depend to a large extent upon the temperament and inherent or acquired tendency to emotivity of the individual, as well as upon the severity of the disease. Chronic

cases, it may be remarked, are more liable to become neurasthenic than those exhibiting a shorter course. Six patients only of the 120 recovered cases could definitely be said to show signs of true neurasthenia when examined 4-6 months after recovery from meningitis; of these six patients, two at least were neurasthenic prior to the attack of cerebro-spinal fever. Of the remainder the following case serves as an example:

The patient was examined six months after recovery from a severe attack of cerebro-spinal fever lasting approximately five weeks. He complained of frequent headache, soreness in the limbs, and of fatigue upon the slightest exertion; his appetite was poor and he slept badly.

Physical Signs.—The patient was thin and perspired freely during the examination, although it was winter. The pupils were somewhat dilated, equal, and reacted sluggishly to light and accommodation. There was a well marked tremor of the outstretched hands, the superficial reflexes were brisk and the knee and ankle jerks exaggerated. No ankle clonus was elicited, and both plantar reflexes were flexor.

Two other patients exhibited a somewhat similar condition; one, in addition, complained of occasional loss of memory. Another recovered case, seen four months after his discharge from hospital, complained of sleeplessness but showed no other evidence of neurasthenia.

A slight tremor of the outstretched hands is frequently observed during the first few months following recovery from the disease.

One patient examined five months after recovery from meningitis closely simulated a case of disseminated sclerosis. The man, aged 26, complained of occasional inability to use the left hand and also of frequent diplopia. On examination there was distinct rotatory nystagmus on lateral deviation of the eyes, together with weakness of the left external rectus muscle. The pupils were somewhat dilated but reacted normally to light and accommodation; the optic discs showed nothing abnormal. There was a coarse tremor of the outstretched hands, more marked on intention, together with some incoördination of the left arm. The left hand-grip was considerably weaker than that on the right; the left supinator, biceps and triceps jerks were brisker and of greater range than those on the opposite side. Both the knee and tendo Achillis jerks were brisk and exaggerated but equal on the two sides; ankle clonus, however, was absent and both plantar reflexes were definitely flexor. The abdominal and epigastric reflexes were also well marked and speech was normal.

The presence of the abdominal reflexes and a bilateral flexor plantar response alone serve to distinguish the above condition from disseminated sclerosis.

Foster and Gaskell mention a recovered case exhibiting exaggerated knee jerks, volitional tremors, weakness of the bladder and pallor of the optic discs.

SPECIAL SENSES

The Eye.—Blindness may result from (1) damage to the structures of the eyeball, (2) permanent changes in the nervous tissues associated with vision.

(1) *Damage to Structures of Eyeball.*—Corneal ulceration may leave permanent opacities, and loss of vision is the usual sequel to irido-choroiditis. This latter complication had occurred in one case of the 120 ; when examined three months after recovery from meningitis he was able only to distinguish light from darkness with the affected eye. Panophthalmitis is almost invariably followed by complete blindness in the affected eye.

A large vitreous haemorrhage, associated with optic neuritis, occurred in one of our cases during the course of illness. When seen three months after recovery the vitreous was practically clear and vision in the affected eye was 6/9 (*vide* p. 206).

(2) *Permanent Changes in the Nervous Structures.*—In adults, blindness of central origin is very rare ; when present, it is usually due to optic atrophy and is permanent and incurable.

In infants suffering from the posterior basic type of the disease, blindness, according to Langmead, develops in about 30 per cent of cases. Although at first the optic discs may exhibit no definite change, optic atrophy usually develops at a later stage. In most instances, the blindness is due to changes in the visual centres situated in the cerebral cortex of the occipital region.

No instance of blindness of nervous origin occurred in the series of cases under review.

The Ear.—Deafness is the most common of the serious sequelae met with at the present day. The disability is almost always bilateral, and if persisting during convalescence, is usually permanent ; some recovery, however, has been known to occur in a few instances after an interval of two or three months.

Below the age of seven or eight years, permanent deafness usually leads to an associated mutism ; even though speech has begun it gradually disappears. Statistics of the proportion of

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acquired deaf mutes who owe their defect to cerebro-spinal meningitis are widely divergent, the number as estimated by different observers varying from 8 to 45 per cent. The condition appears less common in the posterior basic type of the disease than in the more ordinary types. There is little doubt, however, that permanent deafness resulting from cerebro-spinal fever is much less frequent now than formerly. The condition is probably brought about by atrophy of the auditory nerve and possibly some destruction of the cochlea.

Permanent and absolute deafness was present in two cases only of the 120 recovered from cerebro-spinal fever. Partial deafness (20 per cent) of central origin resulted in one other case.

VASO-MOTOR AND SECRETORY DISTURBANCES

In the majority of cases a well-marked tache cérébrale can usually be elicited for many weeks and even months following the disease.

Profuse and easily elicited perspiration, apart from a condition of neurasthenia, was present in some cases of the series up till two or three months after recovery from meningitis.

THE REFLEXES IN RECOVERED CASES

The following observations are the result of a study of 120 cases recovered from the disease and seen at various periods from two months to one year after recovery. One case of hemiplegia is excluded.

Knee Jerks.—In five cases only were the knee jerks found absent, in spite of the employment of the usual methods of reinforcement. Of these five cases, in two patients their absence was dependent upon the presence of definite peripheral neuritis, the tendo Achillis jerks also being absent, together with loss of both epicritic and protopathic sensibility over certain areas of the lower limbs. In two other cases the tendo Achillis jerks also were not elicited, although there was no definite evidence of neuritis. The last case exhibited absent patellar reflexes but the tendo Achillis jerks were brisk.

In 10 cases the response to tapping the ligamentum patellae was very slight.

In 30 cases the knee jerks were distinctly brisk and exaggerated,

but in no instance was this condition associated with either true ankle clonus or a definite extensor plantar reflex.

In the remaining 75 cases the knee jerks could be described as moderate.

Marked inequality in the reflexes of the two sides was noted in three instances only, and was unassociated with any other physical signs.

Tendo Achillis Jerks.—This tendon reflex is usually proportional to that obtained at the knee. In one case only, mentioned above, were the tendo Achillis jerks elicited in the absence of the patellar reflexes. In two instances the tendo Achillis jerks were brisk but the knee jerks excessively slight.

Inequality of the ankle jerks on the respective sides was observed in two cases, one of which also exhibited a corresponding inequality in the knee jerks.

In no instance was true ankle clonus obtained. Three cases showed what might be described as unilateral pseudo-ankle-clonus, unassociated with any signs of an upper neurone lesion.

Plantar Reflexes.—In all cases plantar stimulation yielded a flexor response.

Abdominal Reflexes.—It would appear that cerebro-spinal fever may occasionally lead to permanent loss of the abdominal reflexes. Failure to elicit these reflexes occurred in three cases ; of these, no patient exhibited any other abnormal physical signs and in each they had been obtained in the earlier stages of the attack of cerebro-spinal fever.

In 14 cases the abdominal reflexes were only very slight, while in eight they were more than usually brisk. In all the remaining cases these superficial reflexes were moderate. Inequality was noticed in two cases only.

CONDITIONS OTHER THAN THOSE OF THE NERVOUS SYSTEM AND ORGANS OF SPECIAL SENSE

Heart.—Permanent cardiac changes following cerebro-spinal fever are very rare. Those cases in which endocarditis occurs as a complication almost invariably prove fatal, and in those exhibiting some dilatation of the heart, the organ usually returns to normal with the termination of the pyrexial course. In one of our cases (Case XXV. p. 180), however, persistent tachycardia resulted. The patient when seen three months after recovery from menin-

gitis, exhibited a pulse rate varying between 120 and 140 per minute ; the cardiac impulse was $\frac{1}{4}$ inch internal to the nipple line and the sounds appeared normal. On exertion, the man complained of palpitation, dyspnoea and extreme fatigue even on walking only a short distance.

Phlebitis.—Oedema of one leg, resulting from phlebitis, may persist for a considerable time. This condition is rare in cerebro-spinal fever, but in one of our cases oedema was still apparent after mild exercise three months after recovery from meningitis (*vide* p. 183).

Pyelitis.—Pyelitis may occasionally persist for some time after the termination of meningitis. As a rule, however, it soon disappears.

Nephritis.—This condition, as a direct complication of cerebro-spinal fever, is rare. In one case of our series developing nephritis only during the course of cerebro-spinal fever, on recovery from meningitis all signs of nephritis had disappeared. In some cases, however, a chronic nephritis may persist, the patient being liable to acute exacerbations.

A summary of the more serious sequelae occurring in the series of 120 recovered cases is as follows :

Strabismus	. .	2 cases.
Blindness (peripheral)	.	1 case (one eye).
Monoplegia	. .	1 case (function fully restored about 7 months after recovery from meningitis).
Hemiplegia	. .	2 cases (in one case recovery was nearly complete as regards motor power $7\frac{1}{2}$ months after onset).
Neurasthenia (true)	.	4 cases.
Deafness (absolute)	.	2 cases.
Deafness (partial)	.	1 case.

From this table it will be seen that including strabismus and neurasthenia, 10 patients only of the 120 (8·3 per cent) suffered from serious and more or less permanent sequelae.

Of the military cases recovering from the disease—94 in number—as far as we are aware, it was necessary sooner or later to discharge as medically unfit for further army service in any category whatever 11 cases only (11·7 per cent). Of these, one patient was neurasthenic prior to developing cerebro-spinal fever and, in addition, had double otitis media of old standing ; in the ordinary course of events he would have been discharged quite apart from

the attack of cerebro-spinal fever. In four further cases discharge was also recommended on account of neurasthenia. The presence of permanent deafness accounts for two others, and one patient each was invalided on account of one of the following disabilities : persistent strabismus, blindness (peripheral) of one eye, residual weakness of the foot remaining after hemiplegia, and lastly, in a patient aged 41, persistent pain in the lumbar region on exertion.

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